THE RELATIONSHIP BETWEEN RETINAL AND COGNITVE FUNCITONING IN

SCHIZOPHRENIA

by

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ABSTRACT OF THE THESIS

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The retina may provide a unique window into brain structure and function as an accessible part of the central nervous system. Abnormalities in retinal cell structure and function have been associated with brain pathology (e.g., brain volume loss, cognitive impairment, functional disability) in several neuropsychiatric disorders (e.g., Multiple Sclerosis, Alzheimer's disease, Parkinson's disease). A number of prior studies using flash electroretinography (fERG) have observed a reduction in retinal cell activity in schizophrenia (SZ). Impairments in cognitive functioning are a core feature of SZ and deficits in executive control processes involving prefrontal cortex (PFC) activity (i.e., working memory, attention, executive functioning), are strong indicators of functional capacity. However, it is not known how anomalies in retinal cell signaling may relate to cognitive changes in SZ. This study examined whether retinal cell functioning is related to brain function, as indexed by cognitive function, in SZ, and if these relationships were stronger in particular domains (e.g., PFC dependent functions vs. less PFC dependent functions). Twenty-six SZ participants and 24 healthy controls (HC) completed an fERG protocol and cognitive test battery. fERG measurements included a-wave (photoreceptor cells), b-wave (bipolar-Müller cell cells), and oscillatory potential (OP; amacrine cells)

amplitudes and implicit times. Cognitive tests assessed executive control processes such as attention/speed of information processing, behavior initiation, response inhibition, and working memory, and non-executive control processes such as emotion recognition and discrimination. fERG and cognitive test data were examined for between-group differences. The relationship between fERG variables and cognitive test scores within each group was assessed with Pearson correlations and hierarchical multiple regression analyses. Canonical correlations were also performed to determine if a set of fERG variables was significantly related to a set of cognitive functioning variables. Our results confirm those of prior studies demonstrating anomalies in a-wave and b-wave activity and lower cognitive test performance in SZ, in comparison to controls. In the HC group, a-wave amplitude was correlated with cognitive test scores and OP amplitude was related to cognitive test performance in the SZ group. However, overall, retinal cell activity did not appear to be strongly related to scores on cognitive tasks, regardless of whether or not they involved frontal brain regions. Thus, impairments in retinal and cognitive functioning may reflect distinct disease mechanisms in schizophrenia. Additional studies of larger sample sizes are needed in order to determine the similarity between retinal cell functioning and cognitive functioning in SZ.

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Introduction

Background

During development, the retina and the brain are formed from the same tissue (the neural tube) and thus the retina is considered part of the central nervous system (CNS). Not surprisingly then, similarities exist between retinal and brain structure and function. However, unlike the live brain, the retina can be examined directly using non-invasive techniques. Furthermore, methods for examining retinal structure and function are efficient, cost-effective, and are not limited by low spatial resolution or the use of isotopes. Therefore, the retina may serve as a useful model of CNS structure and function more broadly (i.e., the brain; Silverstein & Rosen, 2015).

Imaging techniques, such as optical coherence tomography (OCT), have been used to examine retinal structure and have identified similarities between the eye and the brain. For example, a loss of retinal ganglion cell axons, referred to as retinal nerve fiber layer (RNFL) thinning, may reflect brain neurodegeneration (W. W. Lee, Tajunisah, Sharmilla, Peyman, & Subrayan, 2013). This relationship has been found in several conditions. In multiple sclerosis (MS; Gordon-Lipkin et al., 2007) and aging populations (Ong et al., 2015), RNFL thinning has been linked to brain volume loss. In both MS and Alzheimer's disease (AD), RNFL thinning corresponds with disease progression and level of cognitive decline (Iseri, Altinas, Tokay, & Yüksel, 2006; Liu et al., 2015; Toledo et al., 2008). Similarly, in Parkinson's disease RNFL thinning is related to visual hallucinations (J.-Y. Lee et al., 2014) and degree of functional disability (Satue et al., 2014; Tian, Zhu, & Liu, 2011).

Flash electroretinography. Given the similarities between the eye and brain in terms of neuronal and neurotransmitter function, it is likely there are also parallels in aspects of activity. A technique that is relevant to exploring this issue is the flash electroretinogram (fERG). The fERG is a non-invasive, brief, and inexpensive technique used to examine retinal functioning. It records an electrical potential evoked by retinal cells in response to light stimuli. The fERG waveform is characterized by a negative a-wave indicative of photoreceptor cell hyperpolarization followed by a positive b-wave arising from bipolar-Müller cell complex depolarization. In photopic (light-adapted) conditions (above 3 cd/m^2), photoreceptor cell activity is indicative of cone functioning, while scotopic (dark-adapted) conditions under (0.001 cd/m^2) primarily capture rod functioning. In mid-level lighting conditions (between 0.001 cd/m^2 and 3 cd/m^2), both rods and cones contribute to the photoreceptor response. During the rising phase of the b-wave a series of high-frequency wavelets are generated called oscillatory potentials (OPs). While it is not known which specific retinal cells are implicated in the generation of OPs, it has been proposed that amacrine cells play a role in their development (Wachtmeister, 1998). For all waveform components, both amplitude and implicit time (i.e., latency) are typically examined (Appendix G; Gagné, Hébert, & Maziade, 2015; J. Lavoie, Maziade, & Hébert, 2014).

fERG abnormalities in retinal cell functioning have been identified in several psychiatric and neuropsychiatric conditions. For example, in patients with seasonal affective disorder (SAD) a decrease in rod sensitivity has been observed in winter months (Hébert, Beattie, Tam, Yatham, & Lam, 2004), but this normalizes in summer months (Hébert, Dumont, & Lachapelle, 2002) or after four weeks of light therapy (M.-P. Lavoie

et al., 2009). In Parkinson's disease, a reduced rod-cone and bipolar cell response has been observed (Nowacka, Lubiński, Honczarenko, Potemkowski, & Safranow, 2015), and an improvement in photoreceptor response following levodopa (L-DOPA) administration has also been demonstrated, indicating an action of dopamine at the level of the retina (Jaffe et al., 1987). Of note, carrier-mediated transport systems at the inner blood-retinal barrier (BRB) allow for the permeability of some drugs, such as L-DOPA (Brandies & Yehuda, 2008; Hosoya, Yamamoto, Akanuma, & Tachikawa, 2010). Furthermore, neurotransmitters such as dopamine (DA) are known to play a role in modulating retinal activity, suggesting fERG may also be useful in the study of schizophrenia (Berson, 2002; Brandies & Yehuda, 2008), where alterations in DA activity have been observed in multiple brain regions (Howes & Kapur, 2009).

Prior studies examining retinal functioning in schizophrenia have shown that patients demonstrate reduced a-wave and b-wave fERG amplitudes during photopic (Balogh, Benedek, & Kéri, 2008; Demmin, Davis, Roché, & Silverstein, 2018; Hébert et al., 2015; Warner, Laugharne, Peet, Brown, & Rogers, 1999) and scotopic conditions (Demmin et al., 2018; Hébert et al., 2015; Warner et al., 1999), along with increased photopic b-wave implicit time, when compared to healthy controls (Hébert et al., 2015; Demmin et al., 2018). In one study, a reduced photopic a-wave amplitude that was observed in schizophrenia patients upon hospital admission for a psychotic symptom exacerbation was significantly normalized (but still reduced) after eight weeks of treatment, suggesting a possible effect of clinical state on retinal activity (Balogh et al., 2008). However, some abnormalities in retinal cell functioning may be trait-related markers of disease susceptibility, as demonstrated by Hébert et al. (2010), who reported

reduced scotopic b-wave amplitude in non-affected offspring of individuals with schizophrenia or bipolar disorder (genetic high risk youth). Very few studies have assessed OPs in schizophrenia and findings from these studies are mixed, likely due to small sample sizes, thus it is unclear whether this fERG waveform component is affected in schizophrenia (Marmor et al., 1988; Raese et al., 1982; Schechter et al., 1987).

Cognitive functioning in schizophrenia. Schizophrenia is associated with neurocognitive impairments in a wide variety of domains (i.e., processing speed, attention, executive functioning, verbal memory and language processing (Bhattacharya, 2014; Fioravanti, Bianchi, & Cinti, 2012; Nuechterlein et al., 2008; Clare, 2005; Cirillo, & Seidman, 2003) and these deficits correspond to structural and functional brain changes (e.g., enlarged ventricles, hypofrontality; see Barch & Ceaser, 2012 and Antonova, Sharma, Morris, & Kumari, 2004 for review). Cognitive functioning has been established as a predictor of everyday functioning in schizophrenia and is correlated with independent residential functioning, social functioning, and vocational success (M. F. Green, Kern, Braff, & Mintz, 2000; Lepage, Bodnar, & Bowie, 2014). Executive functioning, attention, working memory, and processing speed, in particular, have been identified as significant predictors of work skill, interpersonal functions, and community behaviors in schizophrenia (Bowie et al., 2008). These executive control processes are critically dependent on activity within prefrontal cortex (PFC) regions (Kane & Engle, 2002). In schizophrenia, dysregulated activity within the ventrolateral PFC (VLPFC), dorsolateral PFC (DLPFC), and anterior cingulate cortex (ACC) has been associated with impairments in executive control functions, such as deficits in working memory and response inhibition (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009). Furthermore,

the hyperactivity of subcortical DA in schizophrenia thought to underlie positive symptoms (i.e., hallucinations, delusions) may result in a hypofrontality observed in neuroimaging studies in schizophrenia, whereby patients show reduced cerebral blood flow in the PFC that is correlated with low DA metabolite levels (Howes & Kapur, 2009). Thus, dysregulated PFC activity may provide a basis for understanding cognitive deficits related to executive control functions in schizophrenia.

Impairments in social cognition (e.g. emotion perception) have also been observed in schizophrenia (Penn, Sanna, & Roberts, 2007). The processing of facial and emotional stimuli involves activity in regions such as the lateral fusiform gyrus, superior temporal sulcus, and amygdala (Adolphs, Baron-Cohen, & Tranel, 2002; Pinkham, Penn, Perkins, & Lieberman, 2003). In schizophrenia, an overall reduction in limbic activation is observed during emotion identification tasks, however, patients with schizophrenia also demonstrate greater amygdala activation in response to incorrect identification of anger and fearful expressions of emotion in comparison to controls (Raquel E. Gur et al., 2007). Similarly, people with schizophrenia demonstrate increased right amygdala activation when discriminating the intensity of positive emotional faces, and increased overall (bilateral) amygdala activation when discriminating the intensity of negative emotional faces, as compared to controls (Kosaka et al., 2002). Therefore, while emotion processing tasks necessarily involve some degree of top-down activation, in schizophrenia these impairments may be driven by abnormal amygdala activation related to stimulus valence (Raquel E. Gur & Gur, 2010).

Rationale

Studies using fERG have demonstrated reduced retinal activity in schizophrenia (i.e., Balogh et al., 2008; Demmin et al., 2018; Hébert et al., 2015; Warner et al., 1999) and impairments in cognitive functioning have also been established (i.e., (Fioravanti et al., 2012; Minzenberg et al., 2009; Penn et al., 2007). However, the similarities and correlations between degrees of retinal and brain function in schizophrenia have yet to be examined. Furthermore, it is unknown whether retinal function in schizophrenia might be differentially related to specific areas of cognitive function. Therefore, the aim of this study was to investigate the relationship between fERG indices and neuropsychological and cognitive test scores and determine whether these relationships were stronger in particular domains (e.g., cognitive functions mediated by the PFC). Thus, findings from this study will clarify the nature of retinal abnormalities in schizophrenia and the extent to which these changes may be used as markers of different aspects of brain function.

Goals and Hypotheses of the Current Study

The purpose of this study was to determine the degree of covariation between indices of retinal function on the one hand, and of cognitive function on the other. Just as reductions in retinal function in Parkinson's disease parallel changes in brain activity (Brandies & Yehuda, 2008), we hypothesized that reduced retinal activity in schizophrenia would be related to reduced scores on cognitive tasks, and perhaps more strongly related to impairments in some cognitive domains (i.e., primarily PFC mediated functions) compared to others. Therefore, the goal of this study was to examine the links among retinal activity and scores on cognitive tasks associated with activity in both frontal and non-frontal brain regions.

Hypotheses. Three hypotheses were proposed based on the literature reviewed:

1. The schizophrenia group will demonstrate reduced fERG amplitudes and impaired cognitive functioning, when compared with the healthy control group.

2. Greater impairment in cognitive functioning will be associated with more reduced fERG amplitudes in the schizophrenia group.

3. The strength of the relationship between retinal and cognitive functioning will differ across cognitive domains (i.e., executive functions, social cognition). Specifically, retinal functioning will be significantly related to executive control functions (e.g., attention/speed of information processing, behavior initiation, response inhibition, working memory), but will not be related to less top-down driven processes (e.g., emotion recognition and discrimination).

2. Method

Participants

Schizophrenia and schizoaffective disorder (SZ) patients were recruited from Rutgers University Behavioral Health Care (UBHC) Acute Partial Hospital ($n = 18$) and Outpatient programs ($n = 6$), and the Partial Hospital program at Community Care Behavioral Health ($n = 2$). Patient subjects were recruited through presentations at community meetings, interactions with research staff, and staff referrals. Healthy control (HC) participants were recruited from the community. Participants with an active substance use disorder within the last six months, diseases known to affect vision (such as diabetes, high-blood pressure, macular degeneration), or problems with fixation (e.g., amblyopia) were excluded from study participation. The final sample included 26

participants in the SZ group and 24 participants in the HC group. The protocol was approved by the Rutgers IRB (Pro20170000307) and informed consent was obtained for each subject prior to completing the study.

Procedure

Participants completed a diagnostic and symptom interview, a visual acuity test (i.e., Snellen chart viewed binocularly at a distance of 40 cm), a word reading test, a battery of cognitive tests, and the fERG protocol. Patient participants met *DSM–5* diagnostic criteria for schizophrenia or schizoaffective disorder, confirmed using the Structured Clinical Interview for *DSM–5* Axis I Disorders – Research Version (SCID-5; Modules A through D; First et al., 2015). Control participants had no current or recurrent mood, psychotic, or substance use disorder, nor any lifetime or family history (first-degree relatives) of psychotic disorders and were also administered the SCID-5 (Modules A through D). The Positive and Negative Syndrome Scale (PANSS) was used to assess patient symptom severity over the past two weeks (Kay, Fiszbein, & Opfer, 1987). The PANSS is a 30-item structured interview used to evaluate positive (e.g., delusions, hallucinations, disorganized thinking), negative (e.g., flat affect, social withdrawal) and general (e.g., depression, anxiety, hostility) symptoms. However, a five-factor scoring structure was used as it demonstrates good consistency and superior fit to three-factor models (Wallwork, Fortgang, Hashimoto, Weinberger, & Dickinson, 2012). The Wechsler Test of Adult Reading (WTAR; Wechsler, 2001) was administered in order to estimate premorbid intellectual functioning (Dalby & Williams, 1986; R. E. A. Green et al., 2008). The WTAR assesses participants' correct pronunciation of 50 English words. Socioeconomic index (SEI) scores were calculated from participants' report of their

parents' occupations using 1980 census occupational data. Participants who reported smoking within the last month completed the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991), a brief self-report measure of nicotine dependency. Participants were compensated at a rate of $15 per hour of participation and the entire procedure lasted approximately two hours.

Cognitive Battery. The MATRICS Consensus Cognitive Battery (MCCB) was used to assess top-down processes such as attention/speed of processing, behavior initiation (including verbal fluency), and response inhibition. The MCCB is a standardized battery of cognitive tests that was developed to evaluate treatments for cognitive deficits in schizophrenia (Kern et al., 2008; Nuechterlein et al., 2008). However, only those MCCB subtests that measure executive control functions, which primarily depend on activity within the PFC (Diamond, 2013), were included. These tests are described immediately below.

The Symbol Coding subtest of the MCCB (originally developed for the Brief Assessment of Cognition in Schizophrenia (BACS) battery) was administered to assess attention and speed of information processing. In the Symbol Coding subtest, participants were instructed to match numbers to non-meaningful symbols with the use of a key that was provided and were given 90 seconds to complete as many items as possible.

The Category Fluency: Animal Naming and Trial Making Test (TMT): Part A MCCB subtests was administered to evaluate behavior initiation. The Category Fluency: Animal Naming (Animal Naming) subtest is an oral test in which participants were asked to name as many animals as they can in one minute. The TMT Part A required participants to draw a series of lines connecting consecutively numbered circles placed

irregularly on a sheet of paper as quickly as they could. The dependent measure is completion time.

Response inhibition was assessed with the MCCB Continuous Performance Test-Identical Pairs (CPT-IP) subtest, as well as the Stroop task. The CPT-IP is a computer-administered measure of sustained attention in which participants were instructed to respond to consecutive matching numbers by pressing a key. The Stroop paradigm is a measure of selective attention and response inhibition (MacLeod, 1991; Stroop, 1935). Trials consisting of congruent (color name printed in a congruent color), incongruent (color name printed in an incongruent color), and neutral (X's) stimuli were presented on computer screen. Participants were instructed to respond to each stimulus by pressing the key that corresponded to the color of the word (ignoring the word itself). Response time for incongruent conditions was contrasted with response time for neutral conditions. There were 72 trials for each condition, resulting in a total of 216 trials.

The Weschler Memory Scale 3rd Edition (WMS-III)– Spatial Span and Letter-Number Span tasks were administered in order to assess working memory, which has also been linked to PFC function (Kane & Engle, 2002). The WMS-III – Spatial Span assesses nonverbal working memory and required participants to tap cubes that are irregularly spaced on a board in the same or reverse sequence as the test administrator. The WMS-III – Letter-Number Span subtest is a measure of verbal working memory that required participants listen to spoken strings of numbers and letters and mentally reorder them before repeating them to the administrator.

Two subtests within the social cognition domain of the Penn Neuropsychological Test Battery that have been shown to be less reliant on PFC activity and instead involve

an increase in amygdalar and hippocampal activity (i.e., Gur & Gur, 2010) were also administered in order to compare the strength of the relationships between retinal functioning and various types of cognitive functions. The Penn Emotion Identification Test (EMI) subtest measures the ability to decode and correctly identify facial expressions of emotion. In the EMI subtest participants are presented with faces and asked to determine what emotion was being expressed (happiness, sadness, anger, fear, or no emotion). A total of 40 faces are presented (Kohler, Turner, Gur, & Gur, 2004). In the Penn Emotion Differentiation Test (EMD) the ability to decode the intensity of facial expressions of emotion is assessed. Participants were shown two faces at a time that are expressing the same emotion, and were required to determine which face expressed the emotion more intensely (R. E Gur et al., 2006). The administration of the entire cognitive battery (MCCB subtests and emotion processing measures) lasted approximately 90 minutes.

Apparatus

fERG data were collected using RETeval, an FDA-approved device that requires neither corneal contact nor pupil dilation (LKC Technologies, 2007). In preparation for recording, the skin at each electrode site was cleaned using an alcohol pad. A sensor strip skin electrode (with separate regions for a positive, negative, and active ground contacts) was placed 2mm under each eye. The RETeval uses Troland-based stimulation (Td-s), in which, in each block of trials, there is continuous measurement of pupil size, with continuous adjustment of light intensity to ensure that a constant amount of light is delivered through the pupil (LKC Technologies, 2007). Specifically, flash retinal

illuminance (Td-s) is equal to the product of photopic flash luminance (cd-s/m^2) and pupillary area (mm^2).

fERG recording. The RETeval Complete option was used for the fERG protocol to ensure that stimuli complied with the International Society for Clinical Electrophysiology of Vision (ISCEV) recommended standard (Marmor et al., 2009). The protocol included two types of photopic trials using flash stimuli: an 85 Td-s flash presented at a frequency of two hertz (Hz) against a lit background (848 Td; P$_2$) and an 85 Td-s flash presented at a rate of 28.3 Hz against a lit background (848 Td; P$_F$). This second test (flicker test) was given in order to isolate cone functioning, as rods are unable to follow a flicker stimulus at this frequency. Scotopic trials included three types of stimuli: a .28 Td-s flash presented at a frequency of .5 Hz (S$_1$), an 85 Td-s flash presented at a rate of .1 Hz (S$_2$), and a 280 Td-s flash presented at a frequency of .05 Hz (S$_3$), each with no background. An additional photopic condition, a 100 Td-s flash presented at a rate of one Hz with no lit background (P$_1$), which has successfully differentiated schizophrenia patients from healthy controls in previous research from our lab (i.e., Demmin et al., 2018) was added to the protocol. Participants were light adapted (with the lighting conditions of the room) for 30 minutes to several hours prior to photopic testing. Participants were dark adapted for 20 minutes prior to scotopic test administration, as per ISCEV standards. Total recording time was approximately five minutes per eye.

fERG output included measurements of amplitude (in microvolts; mV) and implicit time (i.e., latency, in milliseconds; ms). Amplitude of the a-wave was measured from the baseline to the negative trough of the a-wave. The distance from the a-wave trough to the b-wave peak indicated b-wave amplitude. A-wave and b-wave amplitude and implicit

time were measured for all fERG trials using flash stimuli. However, for the flicker test

(85 Td-s flash, 28.3 Hz, 848 Td background; P_F), fERG waveforms consisted of positive

deflections only and therefore only a single, average amplitude and latency measurement

were obtained. OP waveforms were recorded during the second scotopic test (85 Td-s

flash at .1 Hz; S_2) using an 85 Hz-190 Hz bandpass filter. Amplitude (peak to following

trough) and implicit time (time to peak) were reported for up to five OPs. An overall OP

index was calculated from the sum of each measurement.

Statistical Analyses

Analyses were conducted using SPSS Version 25 (IBM Corp, 2017). Demographic

variables (age, gender, race, ethnicity, parental level of education, parental SEI, visual

acuity) were analyzed in order to assess any significant differences among these variables

between the two groups. However, demographic variables that differed significantly

between groups were not used as covariates in the between-group analyses, in order to

not remove variance that is potentially related to having schizophrenia (e.g., lower

estimated IQ [WTAR], lower SES, etc.). Categorical variables were analyzed using

Pearson's Chi-square test for independence, and independent sample t-tests were used to

test associations between interval and ratio scale variables. In cases where the

homogeneity of variance assumption was violated according to Levene's test for equality

of variances, the corrected degrees of freedom were used to determine significance.

All dependent variables were examined for outliers and trimmed where necessary.

Variables were also examined for normality and transformed (using logarithmic or square

root transforms) as necessary. fERG amplitudes and implicit time were calculated using

the average of left and right eye data. T-scores were derived for executive control

functions (i.e., MCCB subtests and Stroop task) and non-executive control functions (i.e., EMD, EMI). Hotelling's T^2 were calculated from multivariate analyses of variance (MANOVAs) to determine whether there were between-group differences (schizophrenia, healthy control) in fERG amplitude, implicit time, and performance on cognitive tests. Assumptions of independence, homogeneity of covariance matrices (Box's M), homogeneity of variance, no multicollinearity and multivariate normality (Mahalanobis distance) were tested prior to the analyses. Significant T^2 values were followed by independent samples t-tests, using a False Discovery Rate (FDR; Benjamini & Hochberg, 1995) correction ($\alpha = .05$) for multiple comparisons. The False Discovery Rate (FDR) is a correction for multiple comparisons that affords greater power and is more suitable when variables of interest are dependent, as in this analysis. It has been shown that the FDR performs comparably to other methods with few comparisons, and has increased power with a greater number of comparisons (Benjamini & Hochberg, 1995).

The relationship between fERG indices and cognitive functioning was assessed using the general linear model (Cohen, 1988). In these analyses, fERG a-wave amplitude, a-wave implicit time, b-wave amplitude, and b-wave implicit time were averaged across all tests (photopic and scotopic) so that amplitude and implicit time of each waveform component was represented by a single variable. Flicker test and OP fERG data were considered separate variables, as these measurements are reflective of distinct retinal activity (described above). An overall executive control functioning score was also calculated by averaging each individual executive control subtest t-score and a variable

representing non-executive control functioning was derived by averaging emotion identification (EMI) and emotion differentiation (EMD) t-scores.

Pearson correlations were examined between averaged fERG variables and cognitive functioning variables separately for each group. Because these correlations were exploratory in nature, they were not corrected for multiple comparisons. Hierarchical multiple linear regression analyses were performed in order to determine whether a combination of fERG variables predicted executive control functioning scores or social cognitive test scores within each group, after controlling for demographic variables. Data were inspected to ensure that assumptions of linearity (visual inspection of scatterplots), multivariate normality (visual inspection of P-P plots), multicollinearity (VIF and tolerance statistics), independence of errors (Durbin-Watson statistics), and homoscedasticity (visual inspection of scatterplots) were met. Adjusted R^2 values were computed to evaluate the ratio of the sum of squares explained by a regression model and the strength of the associations were interpreted according to coefficient values. Finally, canonical correlations were performed to determine if the set of fERG variables was significantly related to the set of cognitive functioning variables, or to a specific type (e.g., executive control functioning), or specific subsets of these variables (e.g., to attention/speed of processing, behavior generation, response inhibition, and/or working memory scores).

3. Results

Demographic Characteristics

Participants' ages ranged from 21-60. The mean (*SD*) age was 36.88 (10.25) years in the SZ group and 36.46 (12.86) years in the HC group. Six (23.1%) participants in the

SZ group were female and 20 (76.9%) were male. In the HC group 6 (25.0%) of participants were female and 18 (75.0%) were male. Approximately 38.5% of participants in the SZ group identified as African American ($n = 10$), 30.8% identified as Caucasian ($n = 8$), 19.2% identified as Asian ($n = 5$), 23.1% identified as Hispanic ($n = 6$) and 11.4% identified as multiracial or other ($n = 3$). In the HC group 12.5% of participants identified as African American ($n = 3$), 58.3% identified as Caucasian ($n = 14$), 12.5% identified as Asian ($n = 3$), 25.0% identified as Hispanic ($n = 6$) and 16.7% identified as multiracial or other ($n = 4$). Nine SZ participants (34.6%) and two HC participants (8.3%) reported smoking cigarettes and were assessed for their nicotine use within the last month (i.e., FTND; Table 1).

There were no significant differences between groups in terms of age, gender, ethnicity, handedness, parental level of education, or parental SEI. Consistent with previous research indicating that schizophrenia is associated with an increased likelihood of having visual impairment (as compared with other psychotic disorders; Viertiö et al., 2007; Zheng et al., 2015) and that reduced visual acuity is present before diagnosis onset and is a risk factor for the development of schizophrenia (Hayes et al., 2019), SZ patients were characterized by poorer mean visual acuity than controls (measured at 40 cm; $t(45) = 2.60, p = .013$). However, in cases where acuity was less than 20/32 vision was corrected using adjustable lenses for the testing session, and therefore visual acuity was not used as a covariate in the subsequent analyses. A greater proportion of patients in the SZ group reported smoking cigarettes, as compared to the HC group (χ^2 [1, N = 50] = 5.02, $p = .025$). A higher rate of smoking among schizophrenia patients, as compared to other psychiatric and non-psychiatric populations, is also well-documented in previous

literature, and estimates of smoking prevalence range from 58-88% of patients (de Leon

& Diaz, 2005). Estimated premorbid IQ (WTAR standard score) also differed

significantly between groups ($t(46) = -2.99$, $p = .005$), however, this variable was not

used as a covariate in the analyses (for reasons described above). Sample demographic

data are presented in Table 1 (Appendix A).

Clinical Characteristics

In the SZ group, 88.5% ($n = 23$) of participants met criteria for schizophrenia and

11.5% ($n = 3$) met criteria for schizoaffective disorder, according to SCID-5 diagnostic

criteria. Table 2 presents the mean, median, standard deviation, and range of PANSS

factor scores in the SZ group. Scores were derived following a five factor model

(Wallwork et al., 2012), including positive (delusions, unusual thought content,

hallucinations, and grandiosity), negative (blunted affect, lack of spontaneity, motor

retardation, poor rapport, emotional withdrawal, and passive social withdrawal), excited

(hostility, uncooperativeness, poor impulse control, and excitement), depressed (anxiety,

guilt, and somatic concerns), and disorganized/concrete (poor attention, conceptual

disorganization, and difficulties in abstract thinking) symptom factors. Antipsychotic

medications were converted to chlorpromazine equivalent dosages (100 mg; Appendix

B).

Between Group Differences in fERG Amplitude and Implicit Time

Tables 3 and 4 present the mean, median, standard deviation, range, skew, and

kurtosis for the fERG and cognitive test data. Multivariate analyses of variance

(MANOVAs) with group (SZ, HC) as the independent variable were used to assess

differences in fERG amplitude (a-wave, b-wave, flicker test, OP) and implicit time (a-

wave, b-wave, flicker test, OP) measurements. Assumptions of independence, homogeneity of covariance matrices, homogeneity of variance, and no multicollinearity were met; however, one SZ case was removed from the analysis because of an extreme Mahalanobis distance value (multivariate normality assumption). In the first MANOVA assessing differences in fERG amplitude, there was no significant multivariate effect (T^2 = 22.10, $F(11,35)$ = 1.56, p =.154, η^2_p=.33). Univariate tests indicated significant differences across groups in amplitude, and thus were followed with a series of independent samples t-tests using an FDR correction (q = .05) for multiple comparisons. There was a significant difference between groups in P_1 a-wave ($t(45)$ = 2.48, p = .017, adjusted p = .040, d = .72) and b-wave ($t(45)$ = -2.93, p = .005, adjusted p = .040, d = .66) amplitude, P_2 b-wave amplitude ($t(45)$ = -2.45, p = .018, adjusted p = .040, d = .70), S_2 a-wave ($t(46)$ = 2.55, p = .014, adjusted p = .040, d = .74) and b-wave ($t(46)$ = -2.51, p = .016, adjusted p = .040, d = .69) amplitude, and S_3 a-wave ($t(46)$ = 2.30, p = .026, adjusted p = .041, d = .61) and b-wave ($t(46)$ = -2.38, p = .022, adjusted p = .040, d = .70) amplitude, where the SZ group demonstrated reduced amplitudes in all cases. There were no significant differences between groups in P_2 a-wave ($t(45)$ = 1.93, p = .060, adjusted p = .073, d = .55), S_1 b-wave ($t(46)$ = -0.56, p = .580, adjusted p = .580, d = .17), flicker test (P_F) ($t(46)$ = -2.08, p = .044, adjusted p = .061, d = .62), or OP ($t(46)$ = -1.20, p = .235, adjusted p = .259, d = .30) amplitude, however, the SZ group demonstrated reduced amplitudes as compared to the HC group across all stimulus conditions (Appendix C).

A second MANOVA assessed differences in fERG implicit time. Assumptions of independence, homogeneity of variance, and no multicollinearity were met. One SZ cases were removed from the analysis because of an extreme Mahalanobis distance value. A

significant Box's M statistic ($p < .001$) indicated the homogeneity of covariance matrices assumption was not met. According to Levene's tests of equality of error variances, the assumption of equal variances was violated for P_1 a-wave implicit time ($p = .015$) and marginally violated for S_2 b-wave implicit time ($p = .041$), therefore these results should be interpreted with caution. The multivariate effect was significant ($T^2 = 35.06$, $F(11,35) = 2.48$, $p = .020$, $\eta^2_p = .44$) and was followed with a series of independent samples t-tests. After applying the FDR correction, there was one significant difference between groups in implicit time ($t(45) = 3.82$, $p < .001$, adjusted $p = .011$, $d = 1.01$), where P_2 b-wave implicit time was longer in the SZ group as compared to the HC group. There were no significant differences between groups across any other stimulus condition (adjusted ps > .05). The SZ group demonstrated prolonged implicit time in nearly every condition, however, OP implicit time was longer in the HC group as compared to the SZ group (though not significantly different; Appendix C).

Between Group Differences in Cognitive Functioning

Another MANOVA was conducted to assess differences in measures of executive functioning and social cognition. Assumptions of independence, homogeneity of covariance matrices, homogeneity of variance, no collinearity, and multivariate normality were met. There was a multivariate effect of group ($T^2 = 38.93$, $F(9,34) = 3.50$, $p = .004$, $\eta^2_p = .48$). The significant effect was therefore followed by a series of independent samples t-tests, corrected for multiple comparisons. All but one of the independent samples t-tests were significant using an FDR $q = .05$. Scores on measures of attention/speed of processing (Symbol Coding: $t(46) = -3.66$, $p = .001$, adjusted $p = .003$, $d = 1.06$), behavior initiation (Animal Naming: $t(46) = -2.46$, $p = .018$, adjusted $p = .023$,

d = .71; TMT: *t*(46) = -2.51, *p* = .016, adjusted *p* = .023, *d* = .73), response inhibition

(CPT: *t*(44) = -3.40, *p* = .001, adjusted *p* = .003, *d* = 1.00), working memory (Spatial

Span: *t*(46) = -2.82, *p* = .007, adjusted *p* = .013, *d* = .81; LNS: *t*(46) = -4.22, *p* < .001,

adjusted *p* = .003, *d* = 1.22), emotion identification (EMI: *t*(27.77) = -2.37, *p* = .025,

adjusted *p* = .028, *d* = .66), and emotion differentiation (EMD: *t*(46) = -3.13, *p* = .003,

adjusted *p* = .007, *d* = .91) were lower in the SZ group, as compared to the HC group.

There was no significant difference between groups on Stroop task performance,

measuring response inhibition (*t*(48) = -0.97, *p* = .335, adjusted *p* = .335, *d* = .27;

Appendix D).

Relationships Between Retinal and Cognitive Functioning

Pearson correlations were conducted separately for each group to explore the

relationships between a-wave, b-wave, flicker test, and OP amplitudes and implicit time

measurements on the one hand, and performance on executive control functioning and

non-executive control functioning measures on the other. fERG a-wave and b-wave data

were averaged across photopic and scotopic conditions as described above.

In the SZ group, OP implicit time was positively correlated with scores on tests

of working memory (LNS; *r* = .45, *p* = .027) and emotion identification (EMI; *r* = .60, *p*

= .001), and flicker test implicit time was positively correlated with Stroop task (response

inhibition) scores (Stroop; *r* = -.64, *p* < .001), however, these relationships were no

longer significant after removing an outlier from the dataset (*p* > .05). OP amplitude was

negatively correlated with working memory test performance (LNS; *r* = -.41, *p* = .045),

indicating lower OP amplitudes were related to higher working memory scores. There

were no other significant relationships between fERG amplitudes and implicit time, and cognitive test scores observed (ps > .05).

In the HC group, a-wave amplitude was negatively correlated with cognitive test performance, where more pronounced a-wave amplitudes were associated with better performance on subtests assessing attention/speed of processing (Symbol Coding; r = -.50, p = .013), behavior initiation (Animal Naming; r = -.49, p = .016), working memory (Spatial Span; r = -.45, p = .029) and emotion differentiation (EMD; r = -.60, p = .003). Shorter b-wave implicit time was also associated with higher emotion identification scores (EMI; r = -.49, p = .015) scores. There were no other significant correlations with fERG and cognitive test data in the HC group (ps > .05).

fERG Indices as Predictors of Executive Function and Non-Executive Function Scores

Hierarchical multiple regression models were used to determine whether fERG indices were significant predictors of cognitive test performance, over and above demographic variables. First, demographic variables (i.e., age, gender, mean parental education, mean parental SEI, cigarette smoking) were entered into the model, followed by fERG amplitudes, and lastly fERG implicit time variables. Regressions modeling executive control functioning and non-executive control functioning scores separately in each group, are shown in Tables 5 and 6.

In hierarchical multiple regressions that modeled executive control test performance within the SZ group, no assumptions were violated, however, one case was identified as a potentially influential data point (according to Cook's distance values) and was removed. The regression model including both demographic and fERG variables

($F(9,11) = 3.26$, $p = .034$) was significant, and together, these variables explained 72.2%

of the variance in executive function test scores in the SZ group. Specifically, mean

parental SEI ($\beta = .49$, $p = .024$) and smoking status ($\beta = .49$, $p = .025$) were significant

predictors of performance on tests of executive control functions. Amplitude fERG

variables were not identified as significant predictors of executive control test

performance and the addition of these variables ($F(4,11) = 2.99$, $p = .068$) did account for

a significantly greater proportion of variance than the prediction model with demographic

variables only (R^2 change $= .26$, $p = .095$). The regression model including all variables

(demographic, fERG amplitude, and fERG implicit time variables [$F(13,7) = 1.64$, $p =$

.262]) was not significant in predicting executive control functioning test performance in

the SZ group (Appendix E). No assumptions were violated in hierarchical multiple

regressions that modeled non-executive control test performance within the SZ group,

however, the same case was again identified as a potentially influential data point and

was removed (based on Cook's distance value). In the SZ group, none of the models were

significant in predicting non- executive control functioning scores, however, in the

complete model (demographic, fERG amplitude, and fERG implicit time variables)

flicker test implicit time was a significant predictor of test performance ($\beta = .47$, $p =$

.036) and a-wave implicit time was approaching significance ($\beta = -.58$, $p = .051$;

Appendix F).

Assumptions were met for the hierarchical multiple regression modeling executive

control within the HC group, however, one case was removed due to an extreme Cook's

distance value. Among HC participants, none of the models significantly predicted

executive control functioning scores (Appendix E). Assumptions were tested and met for

the hierarchal multiple regression modeling non-executive control test performance in the HC group. Again, none of the overall models predicting non-executive control test performance were significant in the HC group, however, in the first model (demographic variables) age was a significant predictor of non-executive control scores ($\beta = -.54$, $p = .018$; Appendix F).

A canonical correlation analysis was used to explore the relationships between fERG variables and cognitive test scores. Dependent variables were attention/speed of processing (Symbol Coding), behavior initiation (Animal Naming, TMT), response inhibition (CPT, Stroop), working memory (Spatial Span, LNS), and emotion processing (EMI, EMD) scores. The predictor variables included a-wave, b-wave, flicker test, and OP amplitudes and implicit times. With 47 cases in the analysis, the relationship between the sets of variables was not statistically significant, Wilks' $\lambda = .26$, approximate $F(40, 151) = 1.38$, $p = .088$. A second canonical correlation was performed using only those ERG variables which elicited significant between-group differences (P_1 a-wave and b-wave amplitude, P_2 b-wave amplitude, S_2 a-wave and b-wave amplitude, S_3 a-wave and b-wave amplitude, P_2 b-wave implicit time). Again, there were no significant relationships between the two sets of variables (Wilks' $\lambda = .27$, approximate $F(40, 151) = 1.33$, $p = .115$).

4. Discussion

The purpose of this study was to examine the relationship between retinal functioning, as measured by fERG, and cognitive functioning, as measured by neuropsychological test performance, in schizophrenia. Anomalies in retinal cell functioning have been observed in a number of prior studies in schizophrenia (e.g.

Balogh et al., 2008; Demmin et al., 2018; Hébert et al., 2015; Warner et al., 1999) and

impairments in neurocognitive and social cognitive functioning have been well-

established (e.g., Fioravanti et al., 2012; Minzenberg et al., 2009; Penn et al., 2007).

Given prior research demonstrating a link between retinal function and brain changes in

neuropsychiatric populations (e.g., Parkinson's disease; Brandies & Yehuda, 2008), it

was hypothesized that attenuated retinal cell activity in schizophrenia would be related to

impaired performance on cognitive tests. Specifically, a relationship between fERG

amplitudes and executive control processes (i.e., attention/speed of processing, behavior

initiation, response inhibition, working memory) was expected, given that fERG

amplitudes appear to be most affected in schizophrenia and higher-order functions which

depend on activity in frontal brain regions, such as working memory, attention,

processing speed, and executive functioning, are most predictive of social, role, and

community functioning in schizophrenia (e.g., Bowie et al., 2008). Thus, it was

hypothesized that people with schizophrenia would demonstrate reduced fERG

amplitudes and lower cognitive test performance, when compared to healthy controls,

and that the relationship between fERG amplitudes and cognitive test performance would

be strongest on measures of executive control, as compared to tasks that involve less

executive control (i.e., emotion identification and discrimination).

Hypothesis 1: Anomalies in Retinal Cell Functioning in Schizophrenia

Findings from an increasing number of studies indicate that retinal functioning is

impaired in schizophrenia. Most commonly, attenuated a-wave and b-wave amplitudes

have been reported (e.g., Balogh et al., 2008; Demmin et al., 2018; Hébert et al., 2015;

Warner et al., 1999), however, several studies have also observed an increase in b-wave

implicit time (e.g., Demmin et al., 2018; Hébert et al., 2015). The results of the present study confirm these prior reports. In the SZ group, a-wave and b-wave amplitudes were reduced across both light- (P_1, P_2) and dark- (S_2, S_3) adapted conditions. Consistent with our own previous work (i.e., Demmin et al., 2018), we also observed an attenuated response to a flicker stimulus (P_F) in the SZ group, although this finding was no longer statistically significant after controlling for multiple comparisons. Lastly, we observed an increase in photopic b-wave implicit time (test P_2) in the SZ group compared to the HC group, which again parallels our and others' prior results (i.e., Hébert et al., 2015; Demmin et al., 2018).

We did not observe a reduction in OP amplitudes in SZ patients relative to controls, adding to the mixed literature on these waveform anomalies (i.e., Marmor et al., 1988; Raese et al., 1982; Schechter et al., 1987). While relatively little is known about the generation of OPs, and very few studies have examined OPs in schizophrenia to date (i.e., (Marmor et al., 1988; Raese et al., 1982; Schechter et al., 1987), dopaminergic inhibitory activity within amacrine cells is thought to contribute to this response (Wachtmeister, 1998), and thus this waveform component may be affected in schizophrenia. However, measurement of OPs is not consistent among prior studies and bandpass filtering methods for extracting OPs (as was used in this study) may be prone to signal distortion (e.g., phase lag, artifacts, attenuation of OP amplitude; Gauvin et al., 2016). Additionally, though there are usually three main OP peaks, we reported summed OP measurements for up to five peaks in this study (McCulloch et al., 2015). Therefore, the methods by which OP measurements were obtained might have contributed to a lack of between-group differences in our data.

Notably, this study was the first to investigate retinal functioning in schizophrenia using the ISCEV recommended protocol, and our results were largely consistent with previously reported findings, indicating that a number of between-group differences can be observed using this standard protocol. Moreover, these data were collected using RETeval, an ERG device that does not require the use of corneal contact electrodes or pupil dilation, providing additional support for the use of a portable, handheld ERG device for data collection in clinical settings.

Hypothesis 2: Impairments in Cognitive Functioning in Schizophrenia

Deficits in cognitive functioning are a core feature of schizophrenia and have been associated with functional outcome (Green et al., 2000; Lepage, Bodnar, & Bowie, 2014). Impairments in higher-order cognitive functions, such as attention, working memory, processing speed, and executive functions, are especially relevant in determining work functioning, social competence, and community behaviors in schizophrenia (Bowie et al., 2008). In the current study, performance on tasks involving executive control functions and social cognition was examined in SZ patients and compared with that of healthy controls. Across nearly all tests, SZ patients performed significantly worse than controls. An exception to this was on the Stroop task, where patients did not significantly differ from controls in their interference (incongruent – neutral) response time. However, prior studies in schizophrenia indicate that an increase in interference reaction time is not always observed (i.e., Barch, Carter, & Cohen, 2004). Thus, overall, our results are in line with a large body of research demonstrating cognitive deficits in schizophrenia and indicating that these impairments can be observed across a wide variety of domains (e.g., Bhattacharya, 2014; Fioravanti, Bianchi, & Cinti,

2012; Nuechterlein et al., 2008; Clare, 2005; Cirillo, & Seidman, 2003).

Hypothesis 3: Anomalies in Retinal Cell Functioning Predict Impairments in Executive Control Processes in Schizophrenia

As an accessible part of the CNS, the retina may provide a unique window into brain structure and function (Chu, Kolappan, Barnes, Joyce, & Ron, 2012; Jindal, 2015; London et al., 2012; Silverstein & Rosen, 2015). This is supported by research demonstrating a link between reduced retinal cell structure integrity (as measured with OCT) and brain neurodegeneration (e.g., brain volume loss, cognitive impairment, functional disability) in several neuropsychiatric populations (e.g., MS, AD, Parkinson's disease; Silverstein & Rosen, 2015). Furthermore, during fetal development, the retina and the optic nerve mature as extensions of the developing brain. Thus, the retina and the brain are composed of the same tissue and share similar neural functioning (London et al., 2012; Silverstein & Rosen, 2015). For example, DA is released in the retina by amacrine cells, and both D1 and D2 receptor types are present throughout the retina (Witkovsky, 2004). Moreover, an increase in ERG amplitudes has been observed in Parkinson's disease after L-DOPA administration (Jaffe et al., 1987), indicating retinal functioning may be related to dopaminergic activity within the brain in Parkinson's disease and other disorders involving dysregulated dopamine neurotransmission, such as schizophrenia.

These findings suggest that changes in retinal cell function in schizophrenia might be indicative of more widespread impairments in CNS functioning, specifically, neurocognitive functioning. It was hypothesized that a reduction in fERG amplitudes in schizophrenia would be uniquely related to scores on measures of executive control

functions involving frontal brain regions, such as attention/speed of processing, behavior initiation, response inhibition, and working memory. A weaker relationship was expected between retinal cell activity and performance on tasks requiring less executive control, for example, emotion identification and discrimination.

Contrary to these hypotheses, we observed little association between retinal and neurocognitive functioning in the SZ group. However, OP amplitude was significantly correlated with scores on a measure of working memory (LNS) in the patient group, indicating reduced OP amplitudes were associated with better working memory scores. Interestingly, no other relationships between fERG amplitudes or implicit time variables and cognitive test performance were observed in the SZ group.

In the HC group, a-wave amplitude was significantly correlated with performance on a several tasks. Specifically, more pronounced a-wave amplitudes were associated with higher scores on a measure of attention/speed of processing (Symbol Coding), behavior initiation (Animal Naming), working memory (Spatial Span), and emotion discrimination (EMD). Moreover, shortened b-wave implicit time was associated with greater emotion identification (EMI) scores in the control group. Of note, correlations were examined among 17 variables and these analyses were uncorrected, therefore, these observed relationships are in need of replication.

In contrast to our expectations, modeled fERG variables failed to account for a significant portion of neurocognitive test score variance after controlling for demographic variables (age, gender, parental education, parental SEI, smoking status). In general, regression models with fERG variables did not reach significance in either group, regardless of whether the cognitive functions assessed involved more or less executive

control processes. Notably, demographic variables, specifically parental SEI and smoking status, were significant predictors of performance on tests of executive control functioning in the SZ group. Patients who reported smoking cigarettes within the last month performed better on tests of executive control, in comparison to patients who did not smoke cigarettes. This relationship between nicotine use and improved performance on neuropsychological tests in schizophrenia is well-supported by previous literature. Additionally, smoking has been uniquely associated with neurocognitive improvements in schizophrenia, whereas this effect is not observed in bipolar disorder and major depressive disorder patients (Morisano, Wing, Sacco, Arenovich, & George, 2013). The finding that cigarette smoking was associated with enhanced performance on tasks involving greater top-down functioning, but not with performance on tasks requiring less executive control is also consistent with prior work suggesting that cognitive improvement as a result of smoking in schizophrenia might be specific to the higher-order functions such as working memory and attention (Sacco et al., 2005). In the SZ group, patients who reported a higher mean parental SEI also had higher scores on tests of executive control functions. This result is also supported by prior literature indicating that low socioeconomic status (SES) in childhood is associated with lower education attainment and poorer cognitive functioning in adulthood (Luo & Waite, 2005; Turrell et al., 2002). Furthermore, among first-episode psychosis patients parental socioeconomic status has been identified as a significant predictor of global cognition (Lutgens, Lepage, Iyer, & Malla, 2014). While there were no significant differences between groups in parental socioeconomic level, mean parental SEI was somewhat lower in the SZ group and thus may have contributed towards the lower test performance in the patient group.

Although overall models with fERG variables were not significant in predicting non-executive control test performance in the SZ group, some implicit time variables were identified as significant predictors. Specifically, longer flicker test implicit time was associated with higher emotion processing (EMI and EMD) test scores in SZ. This finding is somewhat surprising, as it might be expected that increased response time would be associated with lower cognitive test performance. Additionally, fERG a-wave implicit time was marginally significant ($p = .051$) in predicting non-executive control test scores in the SZ group, whereby shorter implicit time measurements were predictive of higher test scores.

In the HC group, overall models failed to account for a significant portion of variance in cognitive test performance. However, age was identified as a significant predictor of lower non-executive control test scores in the HC group, but only in the first regression model consisting of demographic variables. Research suggests that healthy older adults demonstrate a positivity effect in their attention and memory, associated with less processing of negative emotional stimuli as compared with younger adults (Nashiro, Sakaki, & Mather, 2012). Therefore, older adults in the HC sample might have been less attentive during the presentation of angry, fearful, and sad facial affect stimuli than were younger adults, potentially resulting in decreased accuracy.

Lastly, using canonical correlation analyses, we observed no significant relationships between sets of fERG variables and neurocognitive test scores in the sample as a whole. Together, the results of these analyses suggest that retinal functioning may not be strongly related to frontal lobe mediated cognitive functioning in schizophrenia, or in healthy controls. Likewise, retinal cell activity does not appear to be clearly related to

less PFC dependent cognitive functions. Therefore, while previous research has demonstrated a link between retinal and brain changes in neuropsychiatric populations (i.e., MS, AD, Parkinson's disease; Brandies & Yehuda, 2008; Silverstein & Rosen, 2015), this same relationship may not be as apparent in schizophrenia. One possible explanation for this is that whereas MS, AD, and Parkinson's disease are considered age-related neurodegenerative disorders, with CNS deterioration progressing over time, schizophrenia is often conceptualized as a neurodevelopmental disorder (although some support exists for a degeneration hypothesis; Gupta et al., 2016). Therefore, reductions in retinal cell integrity and function may reflect overall CNS degeneration in affected neuropsychiatric populations, rather than evolving CNS dysfunction related to disease susceptibility. In schizophrenia, impairments in cognitive functioning (e.g., verbal memory, working memory, processing speed) have been observed in first-episode patients who are early in disease course and medication-naïve, and impairments in these domains have also been exhibited in clinical and genetic high-risk samples (Barch et al., 2001; Jahshan, Heaton, Golshan, & Cadenhead, 2010; Saykin et al., 1994; Snitz, 2005). Similarly, anomalies in retinal cell signaling have been observed in non-affected genetic high risk youth (who have a parent with schizophrenia or bipolar disorder), indicating these abnormalities may be indicators of illness risk (i.e., Hébert et al., 2010). Thus, impairments in both retinal and cognitive functioning in schizophrenia may be a consequence of psychosis liability but may not reflect a shared disease process. Additionally, while anomalies in retinal cell functioning in schizophrenia are thought to potentially arise from neurotransmitter dysfunction, such as DA (i.e., J. Lavoie et al., 2014), the exact influence of DA, and other neurotransmitters, within the human retina is

not fully understood. Therefore, since the mechanism by which ERG amplitudes are affected in schizophrenia is unclear, it is not known how these abnormalities might relate to broader CNS dysfunction.

Another possibility is that while retinal degeneration (i.e., as measured with OCT) may be predictive of cognitive functioning in neuropsychiatric populations (i.e., MS, AD; Brandies & Yehuda, 2008; Silverstein & Rosen, 2015), retinal functioning (i.e., as measured with ERG) may not be associated with brain changes. Thus, the link between retinal and brain changes in some disorders may be specific to retinal structural abnormalities. It is also possible that anomalies in retinal cell functioning in schizophrenia are related to other CNS functions, or are a more general indicator of global cognitive decline as opposed to certain cognitive functions (i.e., central executive processes). Therefore, retinal cell functioning may reflect general CNS integrity in schizophrenia, rather than activity within particular brain regions.

Limitations

There are several limitations of the current study. The most significant limitation may be the relatively small sample sizes in this study, which likely lacked power to detect many associations. Nevertheless, the analyses did appear to be sufficiently powered to detect between-group differences in both fERG amplitudes and neurocognitive test performance, consistent with a large body of previous literature suggesting impairments in retinal and cognitive functioning are fairly robust in schizophrenia (e.g., Barch et al., 2001; Demmin et al., 2018; Fioravanti et al., 2012; Hébert et al., 2015; Minzenberg et al., 2009; Penn et al., 2007). A second limitation is the somewhat restricted range of cognitive functions assessed in this study. Though it was hypothesized that attenuated

retinal cell activity would be specifically related to PFC mediated cognitive functions (i.e., executive control processes), as this relationship was not well-supported in our findings it is possible that retinal cell functioning is more strongly associated with other cognitive domains (e.g., memory, perceptual processes), or indicative of overall cognitive functioning (i.e., IQ), and thus a broader cognitive battery might have elicited stronger associations. Lastly, we cannot rule out possible effects of antipsychotic medication on fERG response or cognitive test performance. Although fERG abnormalities have been observed in unaffected offspring of parents with schizophrenia or bipolar disorder (i.e., Hébert et al., 2010), another study reported an improvement in a-wave amplitudes (less attenuated response) in schizophrenia patients following hospitalization for acute psychosis and eight weeks of treatment (Balogh et al., 2008). In addition, in healthy controls, antipsychotic medications have been shown to reduce fERG amplitudes and increase implicit time (Bartel et al., 1990a; Bartel et al., 1990b). Similarly, while some neurocognitive deficits are present in medication-naïve and clinical and genetic high-risk samples (Barch et al., 2001; Jahshan et al., 2010; Saykin et al., 1994; Snitz, 2005), some research suggests that schizophrenia patients who are prescribed more than one antipsychotic, conventional (as opposed to atypical) antipsychotics, or a chlorpromazine equivalent dose of greater than 100 mg per day exhibit poorer cognitive functioning (Hori et al., 2006). Therefore, possible medication effects might have obscured the relationship between retinal and cognitive functioning in our patient sample.

Summary and Future Directions

Anomalies in retinal activity (i.e., Balogh et al., 2008; Demmin et al., 2018; Hébert et al., 2015; Warner et al., 1999) and impairments in cognitive functioning have

been well-established in schizophrenia (i.e., Fioravanti et al., 2012; Minzenberg et al., 2009; Penn et al., 2007). The retina, which extends from brain tissue during fetal development and involves similar neurotransmission, may therefore serve as a useful model of CNS function more broadly in schizophrenia (i.e., the brain; London, Benhar, & Schwartz, 2012; Silverstein & Rosen, 2015). In this study, we investigated the relationship between fERG indices and neurocognitive test performance in order to determine the degree of similarity between retinal and cognitive functioning in schizophrenia. Specifically, we hypothesized that reduced retinal cell responses would be associated with impairments in central executive functions that rely more heavily on activity within frontal brain regions. However, in contrast to our expectations, we observed few relationships between retinal activity and performance on tasks involving more (or less) executive control processes. Overall, a lack of strong evidence indicating an association between impairments in retinal and neurocognitive functioning suggests that these abnormalities may reflect distinct disease mechanisms in schizophrenia. Nevertheless, the similarity between retinal and brain pathology (e.g., brain volume loss, cognitive impairment, functional disability) in several neuropsychiatric disorders (e.g., MS, AD, Parkinson's disease) suggests that the retina may provide an alternative site for investigating changes in brain tissue and function. Furthermore, we observed a number of associations between a-wave amplitude and cognitive test performance in the HC group, and a relationship between OP amplitude and test performance in the SZ group. Thus, these findings warrant further efforts to understand changes in brain structure and function in schizophrenia through direct measurement of the retina. Future studies, with

larger sample sizes, and replication of these findings are needed in order to determine

whether retinal cell functioning parallels broader CNS functioning in schizophrenia.

Appendix A

Table 1

Demographic Characteristics by Group

	SZ (*N* = 26)	HC (*N* = 24)
Variable	*n*(%)	*n*(%)
Gender		
Female	6(23.1%)	6(25.0%)
Male	20(76.9%)	18(75.0%)
Age (Mean[SD])	36.88(10.25)	36.46(12.86)
Range	21, 58	21, 60
Race		
Caucasian	18(30.8%)	14(58.3%)
African-American	10(38.5%)	3(12.5%)
Asian	5(19.2%)	3(12.5%)
Other	3(11.5%)	2(13.3%)
Ethnicity (Hispanic)	6(50.0%)	6(50.0%)
Parental Education (Mean[SD])	13.58(1.80)[a]	13.89(3.17)
Parental SEI (Mean[SD])	32.38(11.71)[a]	55.71(19.86)[c]
Visual Acuity, 40 cm (Mean[SD])	22.38(4.65)[c]	19.60(3.79)
Nicotine Use	9(34.6)	2(8.3)
FTND Total	4.22(2.64)	2.00(2.83)
WTAR IQ Estimate (Mean[SD])	96.79(14.89)[b]	108.33(11.69)

Note. SZ = schizophrenia/schizoaffective disorder, HC = healthy control. FTND = Fagerström Test for Nicotine Dependence, WTAR = Wechsler Test of Adult Reading. [a] *N* = 25, [b] *N* = 24, [c] *N* = 23.

Appendix B

Table 2

Clinical Data SZ Group

Variable	M(SD)	Median	Range
PANSS Factor			
Positive	12.04(4.79)	12.0	15.0
Negative	11.04(3.95)	10.0	15.0
Disorganized/Concrete	8.17(2.53)	8.0	8.0
Excited	7.08(2.86)	6.0	10.0
Depressed	7.52(3.42)	8.0	11.0
CPZ (Mean[SD])	582.49(384.68)	600.0	1600.0

Note. SZ = schizophrenia/schizoaffective disorder. PANSS = Positive and Negative Syndrome Scale, CPZ = chlorpromazine equivalent dose. PANSS factor scores are based on $N = 23$. CPZ equivalent dose mean and SD is based on $N = 25$.

Appendix C

Table 3

fERG Descriptive Statistics by Group

Parameter	SZ (*N* = 26)			HC (*N* = 24)		
	M(SD)	Range	Skew/Kurtosis	M(SD)	Range	Skew/Kurtosis
P$_{1a}$						
Amplitude (μV)	-22.88 (8.14)[a]	39.50	-0.15/1.24	-28.28 (6.88)	24.70	0.06/-0.92
Implicit Time (ms)	15.16 (2.54)[a]	10.45	0.79/-0.03	14.22 (1.40)	5.10	1.29/0.74
P$_{1b}$						
Amplitude (μV)	34.31(15.46)[a]	68.50	1.76/3.84	44.18(14.14)	60.75	0.91/1.34
Implicit Time (ms)	35.80 (1.95)[a]	8.60	0.64/0.38	35.02(1.79)	7.05	-0.42/-0.04
P$_{2a}$						
Amplitude (μV)	-4.74 (2.68)[a]	12.95	-1.06/2.61	-6.03(1.93)	7.55	0.06/-0.07
Implicit Time (ms)	11.77(.99)[a]	4.00	0.23/-0.49	11.77(.85)	3.45	1.02/1.24
P$_{2b}$						
Amplitude (μV)	20.24(8.16)[a]	33.90	0.69/0.27	25.43(6.65)	25.80	0.51/-0.39
Implicit Time (ms)	30.43(1.73)[a]	6.50	0.64/-0.05	28.90(1.27)	5.30	0.50/0.06
P$_F$						
Amplitude (μV)	21.33(8.35)	37.90	0.75/1.56	25.75(5.71)[b]	21.45	0.78/0.39
Implicit Time (ms)	29.35(15.73)	81.80	5.04/25.61	24.77(2.53)[b]	14.20	-3.27/14.17
S$_{1b}$						
Amplitude (μV)	39.10(19.48)	87.95	1.62/2.93	42.09(16.38)	71.45	2.09/4.79
Implicit Time (ms)	98.27(20.27)	102.75	1.58/5.06	88.04(15.53)	69.90	-0.22/0.47
S$_{2a}$						
Amplitude (μV)	-31.40(12.42)	53.35	-0.04/0.38	-39.57(9.37)	36.10	-0.03/-0.15
Implicit Time (ms)	15.96(2.08)	8.95	0.73/0.79	16.46(1.75)	6.50	0.64/-0.10
S$_{2b}$						
Amplitude (μV)	56.53(24.82)	115.95	1.76/4.30	72.79(22.36)	101.75	0.73/1.03
Implicit Time (ms)	52.69(10.70)	48.30	2.32/6.00	51.54(4.14)	15.50	0.27/-0.12
OP						
Amplitude (μV)	40.00(22.35)	90.25	1.59/2.17	47.47(15.05)	63.00	0.09/0.03
Implicit Time (ms)	142.03(18.26)	86.55	-1.94/5.62	149.25(14.49)	39.50	-1.14/0.59
S$_{3a}$						
Amplitude (μV)	-43.66(14.42)	55.75	-0.48/-0.24	-51.53(11.30)	35.90	-0.13/-1.40
Implicit Time (ms)	12.62(1.16)	4.90	0.35/-0.03	12.55(1.07)	3.90	1.24/0.77
S$_{3b}$						
Amplitude (μV)	60.96(25.42)	121.15	1.92/5.12	79.40(27.10)	106.35	0.60/0.05
Implicit Time (ms)	52.74(10.38)	50.60	1.85/4.91	51.20(4.64)	19.75	0.36/0.14

Note. P = photopic, S = scotopic, $_F$ = flicker test, OP = oscillatory potential, $_a$ = a-wave, $_b$ = b-wave, μV = microvolts, ms = milliseconds. [a] *N* = 25, [b] *N* = 23.

Appendix D

Table 4

Cognitive Test Descriptive Statistics by Group

Test	SZ (*N* = 26)			HC (*N* = 24)		
	M(SD)	Range	Skew/ Kurtosis	M(SD)	Range	Skew/ Kurtosis
Attention/Speed of Processing						
Symbol Coding[*]	35.12(11.37)[a]	42.00	0.01/-0.84	48.21(13.29)	44.00	-0.38/-0.22
Behavior Initiation						
Animal Naming[*]	44.67(11.92)	40.00	0.12/-1.21	52.54(10.15)	43.00	-0.26/0.02
Trail-Making Test[*]	36.87(10.37)	43.00	-0.36/0.01	44.83(11.54)	47.00	-0.38/-0.22
Response Inhibition						
CPT[*]	36.35(10.82)[b]	44.00	0.91/0.63	47.09(10.59)[b]	30.00	-0.30/-1.46
Stroop	48.67(9.64)	42.67	-1.34/2.71	51.44(10.38)	51.70	-3.09/11.45
Working Memory						
Spatial Span[*]	42.71(10.46)	41.00	0.11/-0.61	51.71(11.64)	50.00	0.29/0.28
LNS[*]	38.12(10.79)	45.00	-0.35/0.20	50.54(9.58)	29.00	-0.39/-1.26
Emotion Processing						
EMI	47.02(12.99)	68.21	-2.74/10.46	53.22(2.95)	11.00	-0.27/-0.96
EMD	46.18(9.09)	34.35	-0.18/-0.83	54.51(9.28)[c]	32.86	-0.20/-0.99

Note. SZ = schizophrenia/schizoaffective disorder, HC = healthy control.
TMT = Trial Making Test: Part A, CPT = Continuous Performance Test-Identical Pairs,
LNS = Letter-Number Span, EMI = Penn Emotion Identification Test, EMD = Penn
Emotion Differentiation Test.[*] MATRICS Consensus Cognitive Battery subtest. [a] *N* = 24,
[b] *N* = 23, [c] *N* = 22.

Appendix E

Table 5

Hierarchical Regression Analyses Predicting Executive Control Test Performance by Group

Predictor	SZ (*N* = 21)					HC (*N* = 22)				
	B	β	*p*	*F*	R^2	*B*	β	*p*	*F*	R^2
Step 1			**.065**	**2.66**	**.47**			**.913**	**0.29**	**.09**
Age	0.12	0.18	.463			0.08	0.17	.503		
Gender	-3.31	-0.21	.340			-0.33	-0.02	.932		
Parental Education	-0.57	-0.16	.544			0.56	0.29	.407		
Parental SEI	0.35	0.52	.021			-0.05	-0.17	.622		
Smoking Status	7.01	0.49	.025			1.20	0.06	.828		
Step 2			**.034**	**3.26**	**.73**			**.642**	**0.78**	**.39**
a-wave Amplitude	-0.41	-0.53	.078			-0.78	-0.77	.212		
b-wave Amplitude	-0.27	-0.66	.151			-0.08	-0.15	.780		
OP Amplitude	-0.12	-0.37	.110			0.01	0.04	.936		
Flicker Amplitude	0.27	0.34	.366			-0.18	-0.13	.662		
Step 3			**.262**	**1.64**	**.75**			**.636**	**0.83**	**.61**
a-wave Implicit Time	0.05	0.01	.982			-8.00	-0.96	.098		
b-wave Implicit Time	-0.10	-0.08	.791			0.17	0.09	.811		
OP Implicit Time	0.06	0.16	.655			-0.27	-0.43	.437		
Flicker Implicit Time	0.28	0.05	.862			-1.65	-0.69	.170		

Note. SZ = schizophrenia/schizoaffective disorder, HC = healthy control. OP = oscillatory potential.

Appendix F

Table 6

Hierarchical Regression Analyses Predicting Non-Executive Control Test Performance by Group

Predictor	SZ (*N* = 23)					HC (*N* = 22)				
	B	β	*p*	*F*	*R²*	*B*	β	*p*	*F*	*R²*
Step 1			**.699**	**0.60**	**.15**			**.130**	**2.02**	**.39**
Age	-0.11	-0.13	.650			-0.17	-0.54	.018		
Gender	-0.06	-0.00	.991			2.29	0.25	.261		
Parental Education	-2.09	-0.44	.168			-0.42	-0.32	.247		
Parental SEI	-0.04	-0.05	.856			0.02	0.11	.691		
Smoking Status	-0.17	-0.01	.971			-2.44	-0.17	.421		
Step 2			**.440**	**1.07**	**.43**			**.327**	**1.30**	**.49**
a-wave Amplitude	-0.73	-0.70	.073			-0.23	-0.34	.464		
b-wave Amplitude	-0.30	-0.54	.339			-0.05	-0.16	.760		
OP Amplitude	-0.12	-0.29	.327			0.01	0.04	.922		
Flicker Amplitude	0.11	0.10	.840			0.13	0.17	.591		
Step 3			**.018**	**4.24**	**.86**			**.385**	**1.25**	**.67**
a-wave Implicit Time	-4.51	-0.58	.051			-2.57	-0.47	.130		
b-wave Implicit Time	-0.63	-0.39	.064			-0.24	-0.18	.568		
OP Implicit Time	0.12	0.24	.247			0.03	0.06	.876		
Flicker Implicit Time	3.33	0.47	.036			-0.05	-0.03	.927		

Note. SZ = schizophrenia/schizoaffective disorder, HC = healthy control. OP = oscillatory potential.
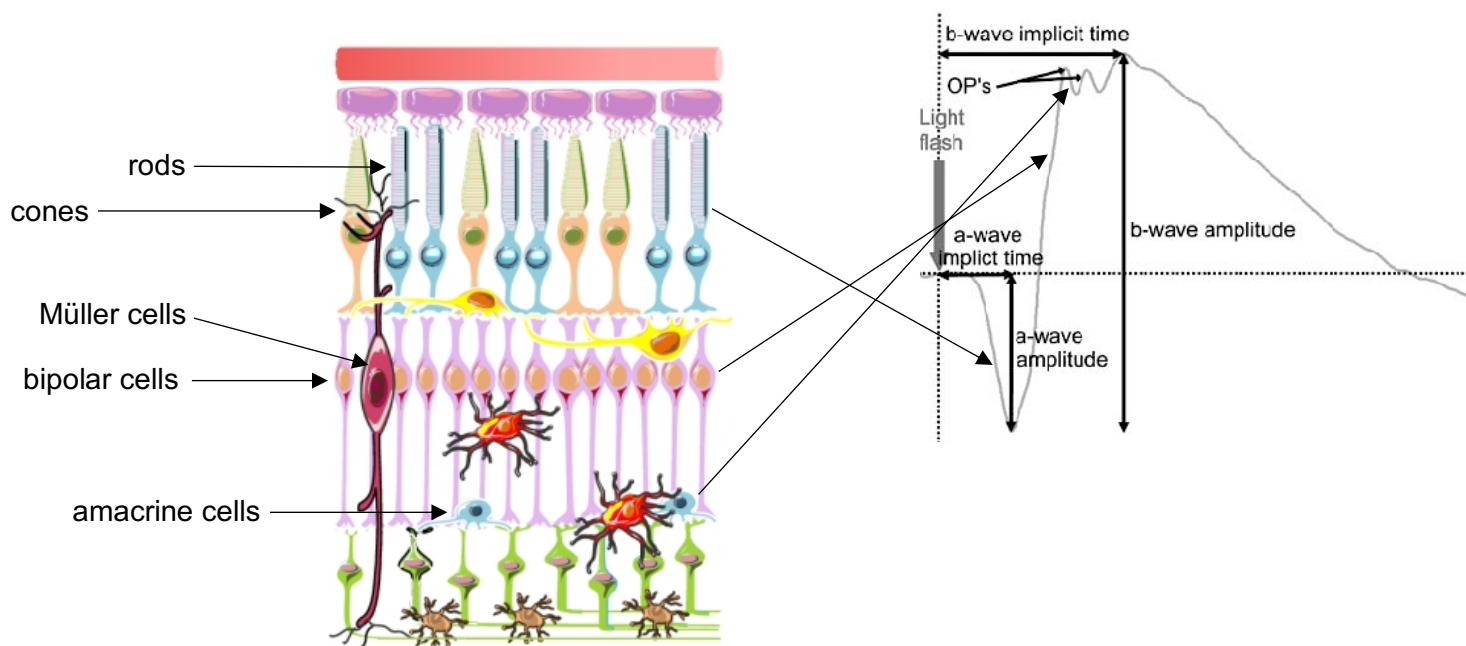
Appendix G

Figure 1. Retinal cellular structure and fERG waveform response. The negative fERG a-wave is driven by photoreceptor (rod and cone) hyperpolarization. Bipolar-Müller cell complex depolarization generates a positive b-wave. Oscillatory potentials (OPs) are observed on the rise of the b-wave and are thought to involve activity of amacrine cells (Wachtmeister, 1998). Both amplitude and implicit time (i.e., latency) of each fERG waveform component can be examined.

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