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Electroretinographic Anomalies in Schizophrenia

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Flash electroretinography (fERG) has been used to identify anomalies in retinal cell function in schizophrenia. Several consistent findings have now emerged, but several potentially important parameters have not yet been investigated. In this study, we recorded light- (photopic) and dark-adapted (scotopic) fERG data from 25 schizophrenia patients and 25 healthy control subjects to (1) determine if past key findings on abnormal photoreceptor and bipolar cell signaling could be replicated; (2) for the first time, examine retinal ganglion cell functioning using the photopic negative response of the fERG; (3) also for the first time, determine responsiveness of schizophrenia patients to a flickering stimulus, as an additional method to isolate cone photoreceptor function; and (4) determine if schizophrenia-related changes in the fERG could be detected using a portable hand-held ERG device. In both photopic and scotopic conditions, schizophrenia patients demonstrated weakened photoreceptor and bipolar cell activations that were most pronounced in response to the most intense stimuli. A reduced cone response to a flicker stimulus and attenuation in ganglion cell activity were also observed in the schizophrenia group. In general, groups did not differ in implicit time of retinal cell responses. These findings (1) replicate and extend prior studies demonstrating reduced photoreceptor (both rod and cone) and bipolar cell functioning in schizophrenia; (2) indicate that retinal ganglion function abnormality can also be detected using fERG; and (3) indicate that these anomalies can be detected using a portable testing device, thereby opening up possibilities for more routine administration of ERG testing.

General Scientific Summary

This article describes a study of retinal cell function anomalies in schizophrenia, as demonstrated by flash electroretinography (fERG). It extends the small number of prior studies in this area in several important ways. For example, it is the first study to report an altered photopic negative response (PhNR) in schizophrenia, which is consistent with previous, but more ambiguous, findings suggesting a ganglionic dysfunction (e.g., lower contrast sensitivity) in schizophrenia. It also demonstrates that these effects can be detected using a portable, handheld ERG device, which opens up possibilities for more routine clinical and research ERG testing.

Keywords: electroretinography, ERG, schizophrenia, retina, perception

The retina is a component of the central nervous system (CNS) that develops from the same tissue as the brain (the ectoderm). The flash electroretinogram (fERG) is a noninvasive, brief technique that is typically used to examine retinal functioning in individuals with retinal disease (e.g., rod and cone dystrophies). However, fERG has also proven to be useful in identifying functional anomalies in neurological and psychiatric populations, where, in many cases, changes in retinal activity correlate with changes in cortical

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functioning, with both relying on similar neurophysiological (including neurotransmitter) mechanisms (J. Lavoie, Maziade, & Hébert, 2014). The nature of these relationships is not well understood at this point (i.e., whether they are causal and if so in which direction, or whether retinal and brain physiology changes are independent manifestations of the same genetic and/or other factors that affect the CNS). However, an emerging consensus in psychiatry and neuro-ophthalmology is that the retina provides a window into brain function that can be useful for understanding brain pathophysiology and for developing biomarkers of illness progression and possibly treatment response (Blokhuis et al., 2016; Chu, Kolappan, Barnes, Joyce, & Ron, 2012; Dhillon & Dhillon, 2008; Frohman et al., 2008; Hyett & Parker, 2013; Jindal, 2015; J. Lavoie et al., 2014; London, Benhar, & Schwartz, 2013; Msall, 2006; Roth, 2015; Schönfeldt-Lecuona et al., 2016; Silverstein & Rosen, 2015).

Flash ERG records electrical potentials generated by retinal cells in response to light stimuli. ERG recordings in photopic (light-adapted, and rod-saturated) conditions are mainly indicative of cone functioning, whereas data from scotopic (dark-adapted) conditions primarily reflect rod functioning. 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. An additional waveform, the photopic negative response (PhNR; Machida, 2012; Viswanathan, Frishman, Robson, Harwerth, & Smith, 1999) occurs after the b-wave under specific photopic conditions, and is generated by retinal ganglion cells (see Figures 1 and 2). Both the amplitude and implicit time (also known as *latency* or *time-to-response peak*) of these components are typically examined (Hébert, Mérette, Paccalet, Gagné, & Maziade, 2017; J. Lavoie et al., 2014; M.-P. Lavoie et al., 2009; Nowacka, Lubiński, Honcza-

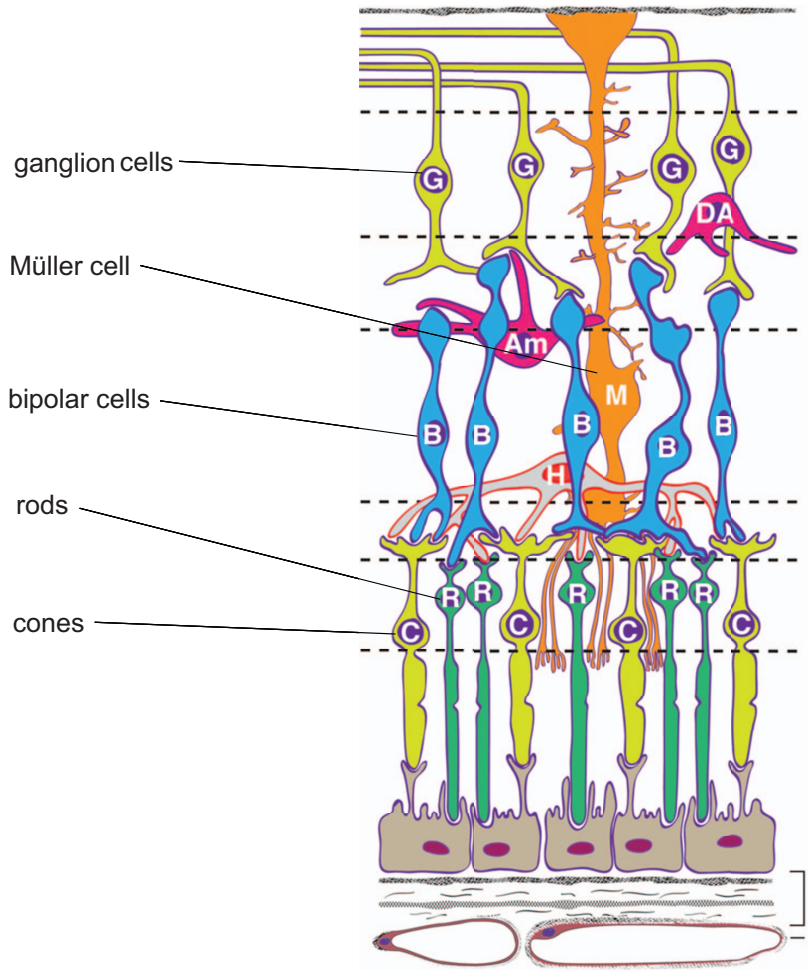

Figure 1. Retinal cellular structure. The negative ERG a-wave is driven by photoreceptor (rod and cone) hyperpolarization. Bipolar-Müller cell complex depolarization generates a positive b-wave. The photopic negative response reflects the activity of retinal ganglion cells. H = horizontal cell, Am = amacrine cell, DA = displaced amacrine cell and M = Müller cell. Image reproduced from Figure 2C in: "Spatial Distribution of the Pathways of Cholesterol Homeostasis in Human Retina," by W. Zheng, R. E. Reem, S. Omarova, S. Huang, P. L. DiPatre, C. D. Charvet, . . . I. A. Pikuleva, 2012, *PloS ONE, 7*(5), e37926. https://doi.org/10.1371/journal.pone.0037926 via a Creative Commons Attribution (CC BY) license. See the online article for the color version of this figure.

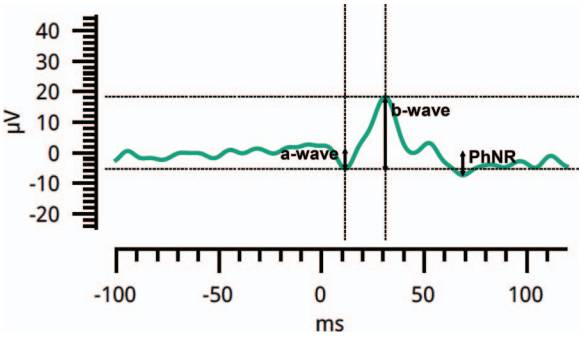

Figure 2. Flash ERG waveform, including the photopic negative response (PhNR). The PhNR follows the b-wave in a cone ERG and reflects the activity of retinal ganglion cells. See the online article for the color version of this figure.

renko, Potemkowski, & Safranow, 2015; Pescosolido, Fazio, & Rusciano, 2014; Realmuto, Purple, Knobloch, & Ritvo, 1989).

Prior studies using fERG in schizophrenia and in high-risk samples have demonstrated multiple anomalies in retinal cell function, with the data suggesting both trait- and state-related changes. For example, both Balogh, Benedek, and Kéri (2008) and Warner, Laugharne, Peet, Brown, and Rogers (1999) demonstrated reduced a-wave amplitude in schizophrenia patients during photopic conditions when compared with healthy controls (Balogh et al., 2008; Warner et al., 1999). Warner et al. (1999) also found decreased a-wave and b-wave amplitudes during scotopic conditions when comparing schizophrenia patients to healthy controls (Warner et al., 1999). In the largest ERG study of schizophrenia to date, Hébert et al. (2015) reported abnormally reduced photopic a-wave and b-wave amplitudes, scotopic b-wave amplitude, mixed rod-cone b-wave amplitude, and increased photopic b-wave implicit times compared to healthy controls (Hébert et al., 2015). Moreover, Balogh et al. (2008) demonstrated that photopic a-wave amplitude reductions were most clearly observed in schizophrenia patients upon hospital admission for a psychotic symptom exacerbation, whereas ERG parameters approached normal levels (but were not completely normal) after eight weeks of treatment, suggesting an effect of clinical state. At least some of these anomalies are related to the diathesis for a serious mental illness, as shown by Hébert et al. (Hébert et al., 2010), who reported reduced scotopic b-wave maximal amplitude in a sample of nonaffected genetic high-risk youth (offspring of parents with schizophrenia or bipolar disorder), compared to controls. Taken together, these data suggest that photoreceptor activity as reflected in the a-wave response may be a state marker for schizophrenia whereas bipolar cell activity as reflected in the b-wave may reflect trait or diathesis aspects of the disorder. Further clarity on which aspects of the fERG are associated with schizophrenia requires replication and extension of past findings, however, because only a limited range of conditions has been studied in schizophrenia so far.

In this study, we recorded fERG data under both photopic and scotopic conditions, and included conditions not used in prior studies, including a flickering stimulus, which is an additional method to isolate cone functioning. We also report, for the first time, on retinal ganglion cell activity as assessed via the PhNR. PhNR is a potentially important variable for schizophrenia because abnormal activity in retinal ganglion cells has been assumed to exist in schizophrenia on the basis of contrast sensitivity (conditional stimulus [CS]) studies (Skottun & Skoyles, 2007), but psychophysical methods such as CS do not isolate ganglion cell function (i.e., there is also likely cortical involvement; Hayes & Merigan, 2007; Silverstein, 2016; Silverstein, Demmin, & Bednar, 2017; Virsu & Rovamo, 1979) and test data can be confounded by generalized deficit issues such as reduced or variable motivation and attention. In contrast, the PhNR has been localized to retinal ganglion cells in primates (Machida, 2012). Finally, we demonstrate the extent to which differences between people with schizophrenia and controls can be observed using a portable, hand-held device for generating the fERG.

Method

Participants

ERG data were collected on 25 patients with schizophrenia and 25 healthy controls (see Table 1). Patients were recruited from Rutgers University Behavioral Health Care's adult inpatient unit ($n = 5$), partial hospital programs ($n = 16$), and outpatient program ($n = 4$). At the time of testing all but one patient was prescribed psychiatric medication. Healthy control participants were recruited from the community via posted flyers and Internet advertisements. All participants were between the ages of 18 and 60 years old. Participants with an active substance use disorder within the last 6 months, diseases known to affect vision (such as diabetes, hypertension, macular degeneration), or problems with

Table 1
Demographic Variables by Group

Variable	SCZ ($N = 25$) *n* (%)	HC ($N = 25$) *n* (%)
Gender		
Female	4 (16%)	7 (28%)
Male	21 (84%)	18 (72%)
Age (*M* [*SD*])	36.80 (10.83)	32.60 (11.91)
Range	20, 58	18, 60
18–32	9 (36%)	15 (60%)
33–46	10 (40%)	7 (28%)
47–60	6 (24%)	3 (12%)
Education (*M* [*SD*])	13.32 (2.12)	14.88 (2.03)
Race		
Caucasian	13 (52%)	14 (56%)
African American	7 (28%)	7 (28%)
Asian	5 (20%)	3 (12%)
Other	0 (0%)	1 (4%)
Ethnicity		
Hispanic	5 (20%)	5 (20%)
CPZ (*M* [*SD*])	588.79 (448.68)	
PANSS Factor (*M* [*SD*])		
Positive	10.64 (4.09)	
Negative	14.24 (5.21)	
Cognitive	11.16 (3.21)	
Excitement	6.92 (2.50)	
Depression	13.08 (4.88)	

Note. All but one patient was taking antipsychotic medication, CPZ equivalent dose mean and standard deviation is based on $N = 24$. SCZ = schizophrenia; HC = healthy control; CPZ = chlorpromazine equivalent dose; PANSS = Positive and Negative Syndrome Scale.

fixation (e.g., strabismus, nystagmus) were excluded from study participation.

Procedure

Participants completed a diagnostic interview, symptom interview, visual acuity testing, and the ERG protocol (described below). Schizophrenia diagnoses were confirmed using the Structured Clinical Interview for *DSM–IV* Axis I Disorders (SCID-IV; First, Spitzer, Gibbon, & Williams, 2002). Control subjects were administered the SCID Non-patient edition to assess for the presence of mood or psychotic disorders (Modules A through D; First et al., 2002). The Positive and Negative Syndrome Scale (PANSS) was used to assess patient symptom severity over the last 2 weeks (Kay, Fiszbein, & Opler, 1987). PANSS symptom dimension scores were generated based on a five-factor model comprising positive, negative, cognitive, excitement, and depression factors (Kay & Sevy, 1990; Lindenmayer, Bernstein-Hyman, Grochowski, & Bark, 1995). After the interviews, which lasted between 30 min and 90 min in all cases, each subject was further light adapted for 5 min in the testing room and then tested with the light-adapted (photopic) tests as described below. Subsequently, subjects were dark adapted for 10 min before the dark adapted (scotopic) tests.

Diagnostic and symptom interviews were conducted by trained research assistants who had achieved high interrater reliability ($\kappa > .80$) on the SCID-IV and the PANSS (intraclass correlation coefficient $>.80$) with other interviewers and faculty-level schizophrenia researchers at the Division of Schizophrenia Research at Rutgers on gold standard training videos. Additionally, all clinical data were reviewed by clinical raters and two experienced research psychologists at a weekly diagnostic consensus meeting. The study was approved by the Rutgers Institutional Review Board (Pro20150002281), and written informed consent was obtained from each participant. Participants received monetary compensation for their participation.

Apparatus. ERG data were collected using the RETeval device, an FDA-approved instrument that requires neither corneal contact nor pupil dilation (LKC Technologies, Gaithersburg, MD). In preparation for recording, the skin at each electrode site was cleaned using an alcohol pad. An adhesive sensor strip containing positive, negative, and ground electrodes was then placed 2 mm under each eye. The RETeval protocol uses Troland-based stimulation, in which there is continuous measurement of pupil size and adjustment of light intensity so that a constant number of photons reach the retina in each trial within each condition (i.e., constant retinal illuminance, rather than constant stimulus luminance, to compensate for changes in pupil size; Davis, Kraszewska, & Manning, 2017; Kato, Kondo, Sugimoto, Ikesugi, & Matsubara, 2015). Specifically, flash retinal illuminance (Td · s) is equal to the product of photopic flash luminance (cd · s/m^2) and pupillary area (mm^2). The electrical potentials were recorded at a sampling rate of approximately 2 kHz.

ERG parameters and dependent variables. The choice of values for light intensity, color, and flash duration were primarily based on values associated with significant between-group discrimination in the studies cited above, and in a publicly available patent application (WO 2014/138987) from which data on schizophrenia have begun to be published (e.g., Hébert et al., 2015), as well as from fERG studies of people with retinal disorders. For light adapted testing, a 100 Td · s flash stimulus was used in two of the conditions because this is approximately midway between the dimmest and middle luminance values in schizophrenia studies reported in the patent application. The first of these stimuli used a 1 Hz repetition rate and no background luminance (P_1). No background was used to maximize the pupillary response and because previous studies in diabetic retinopathy have shown improved detection of this condition when there is no background light (Bresnick & Palta, 1987; Tahara, Matsuura, & Otori, 1993). Another condition (P_2) used a 100 Td·s flash stimulus with a 340 Td background to be more similar (though with a less intense background) to prior fERG studies in schizophrenia (Balogh et al., 2008; Hébert et al., 2017; Warner et al., 1999) and a faster stimulus presentation rate (2 Hz) to reduce testing time. A 58 Td·s red stimulus with a 380 Td blue background, presented at 3.4 Hz (P_{PhNR}), was selected to examine the retinal ganglion cell response as measured by the PhNR. In addition to these flash conditions, we included a condition with an 85 Td·s flickering (at 28.3 Hz) stimulus (P_F). This test has not been previously used in psychiatric studies; however, it is an International Society for Clinical Electrophysiology of Vision (ISCEV) standard test (Burguera, Vilela, Traba, Ameave, & Vallet, 1990) that is primarily a measure of bipolar cell response, and that was included as an additional method to isolate cone activity. Whereas rods cannot follow a flicker stimulus faster than 20 Hz, faster recovery times enable cone cells to follow a stimulus at higher frequencies (Young, Eggenberger, & Kaufman, 2012).

The scotopic tests in this study were 2.8 Td·s (.25 Hz, S_1), 28 Td·s (.1 Hz, S_2), and 280 Td·s (.05 Hz, S_3) white flashes without a background light. The middle stimulus is equivalent to the stimulus reported in the patent application to best discriminate schizophrenia from control subjects. We added conditions that were 10x dimmer and 10x brighter, to more fully explore between-groups differences as a function of light intensity (see Table 2).

Flash ERG output included measurements of amplitude (in microvolts; μV) 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, as per convention (Creel, 2015). Amplitude of the b-wave was measured as the voltage difference from the a-wave through to the b-wave peak (Creel, 2015). Implicit time measurements for each component were measured from flash onset to the response peak (or trough; McCulloch et al., 2015), analogous to latency measurements of visual evoked potentials (VEPs; American Clinical Neurophysiology Society, 2006). Amplitudes and implicit times were measured for all fERG conditions using flash stimuli. These variables represent the strength and the speed of retinal cell response, respectively, and both have consistently been found to be abnormal in multiple forms of retinal disease (Creel, 2015; Pescosolido et al., 2014). The stimulus for the photopic flicker test is sufficiently fast that the fERG response is not characterized by separate a-wave and b-wave responses (see Figure 3) and therefore only a peak-to-peak amplitude and implicit time (i.e., average time between positive peaks) measurement were obtained for this condition. PhNR amplitude was recorded from baseline to PhNR trough and implicit time was measured from stimulus onset to PhNR trough (Kizawa, Machida, Kobayashi, Gotoh, & Kurosaka, 2006). For the PhNR, we restricted our analyses to the two most conceptually relevant indices:

Table 2
FERG Test Conditions

Test	Cell type	Flash luminance energy	Background luminance	Number of flashes
P_{1a}	Cones	100 Td·s at 1 Hz	None	30
P_{1b}	Bipolar cells			
P_{PhNRa}	Cones	58 Td·s, Red at 3.4 Hz	380 Td, Blue	100
P_{PhNRb}	Bipolar cells			
P_{PhNR}	Ganglion cells			
P_{2a}	Cones	100 Td·s at 2 Hz	340 Td	30
P_{2b}	Bipolar cells			
P_F	Cones	85 Td·s at 28.3 Hz	848 Td	141–424
S_{1a}	Rods	2.8 Td·s at .25 Hz	None	5
S_{1b}	Bipolar cells			
S_{2a}	Mixed rods-cones	28 Td·s at .1 Hz	None	5
S_{2b}	Bipolar cells			
S_{3a}	Mixed rods-cones	280 Td·s at .05 Hz	None	5
S_{3b}	Bipolar cells			

Note. P = photopic; S = scotopic; $_a$ = a-wave; $_b$ = b-wave; $_{PhNR}$ = photopic negative response; $_F$ = flicker test.

(1) the minimum amplitude of the post b-wave negative deflection and (2) the negativity of the deflection at 72 ms poststimulus, the time point at which PhNR is generally considered, in the ophthalmology literature, to be maximal (assuming no conduction delays). Because it cannot necessarily be assumed, however, based on past studies of a- and b-wave implicit time in schizophrenia, that there would be no delays in the PhNR in schizophrenia, both metrics were used. In addition to waveform characteristics, we also recorded pupil diameter prior to the onset of each condition, and the pupillary response (change in diameter) to each light stimulus. Testing time was approximately 4 min per eye for each lighting condition (and so, ~16 min to test both eyes in photopic and scotopic conditions).

Statistical analyses. Group differences in demographic variables were assessed with independent samples *t* tests and chi-square tests of independence. To examine fERG a-wave and b-wave amplitudes for photopic and scotopic conditions, 2 (group) × 3 (stimulus condition) mixed-model analyses of variance (ANOVAs), with repeated measures on the stimulus condition factors, were conducted for each condition type (photopic, scotopic), with amplitudes (a-wave, b-wave) as the dependent variables. Implicit times for a-waves and b-waves were also examined, with similarly structured ANOVAs. Regression coefficients for scotopic a-wave and b-wave amplitudes, across the three conditions of monotonically increasing luminance, were calculated individually for each participant and compared between groups in two separate independent samples *t* tests. Flicker test, PhNR amplitude, and pupillary response data were also analyzed using independent samples *t* tests. For the pupillary response data, the alpha trimmed mean and standard deviations were used for each condition. Correlations between fERG variables (a-wave amplitudes and implicit times, b-wave amplitudes and implicit times, PhNR amplitudes and implicit times) and PANSS symptom dimension total scores, as well as antipsychotic medication dosage (in chlorpromazine equivalent dosages), were also performed, but these analyses were exploratory. As such, *p* values from both uncorrected and false discovery rate (FDR; Benjamini & Hochberg, 1995) corrected correlations are reported. Amplitude and implicit time variables were calculated using averages of left and right eye data. In cases in which data from both eyes were not obtained ($n = 2$), data from a single eye were used. Dependent variable data were tested to ensure they did not violate statistical test assumptions. In cases of violations of sphericity in repeated measures data, Greenhouse–Geisser corrected statistical values are reported. Significant interactions were further explored with post hoc independent samples *t* tests, whose *p* values were adjusted using the FDR method to control for multiple analyses.

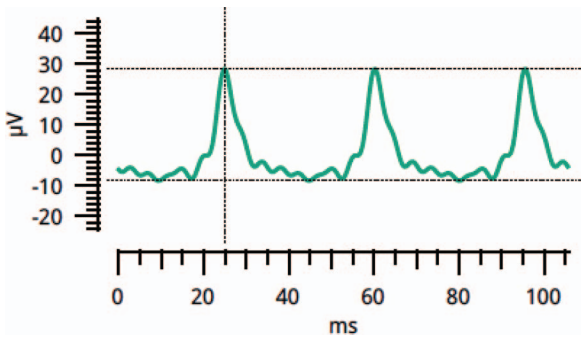

Figure 3. Flash ERG waveform in response to a flicker test stimulus (85 Td·s at 28.3 Hz), consisting of only positive deflections. See the online article for the color version of this figure.

Results

Descriptive Statistics

Table 1 presents demographic data for the schizophrenia and control groups. There were no significant differences between samples in terms of demographic variables.

ERG Amplitude

Photopic conditions. For a-wave amplitude, there were significant main effects of stimulus condition ($p < .001$, $\eta_p^2 = .93$) and group ($p = .013$, $\eta_p^2 = .12$), which were qualified by a

significant Group × Condition interaction, $F(1.23,59.11) = 7.39$, $p = .005$, $\eta_p^2 = .13$, where the degree to which a-wave amplitude was reduced in schizophrenia relative to the control group differed across conditions. Two of the post hoc tests were significant after FDR adjustment (cutoff = 0.03). There was a significant difference between groups in a-wave amplitude for Condition P_1 (100 Td·s at 1 Hz, unlit background; $t[48] = 2.86$, $p = .006$, $d = .81$, 95% CI [.23, 1.39]) and Condition P_{PhNR} (58 Td·s red at 3.4 Hz, blue background; $t[48] = 2.33$, $p = .024$, $d = .66$, 95% CI [.09, 1.23]), with the schizophrenia group demonstrating reduced a-wave amplitudes in both cases. Results are displayed in Figure 4.

For b-wave amplitude during photopic conditions there were also significant main effects of stimulus condition ($p < .001$, $\eta_p^2 = .84$) and group ($p = .010$, $\eta_p^2 = .13$) and a significant Group × Condition interaction, $F(1.65,79.26) = 6.98$, $p = .003$, $\eta_p^2 = .13$. There was a significant difference between groups in b-wave amplitude for Conditions P_1, $t(48) = -2.92$, $p = .005$, $d = .83$, 95% CI [.25, 1.40], and P_2 (100 Td·s at 2 Hz, 340 Td background; $t[48] = -2.69$, $p = .010$, $d = .76$, 95% CI [.19, 1.33]), with the schizophrenia group demonstrating reduced amplitudes in both cases (see Figure 5).

Scotopic conditions. For a-wave amplitude there was a significant main effect of stimulus condition ($p < .001$, $\eta_p^2 = .89$) and a significant Group × Condition interaction, $F(1.58,74.46) = 14.50$, $p < .001$, $\eta_p^2 = .24$. Follow-up comparisons indicated a significant group difference in a-wave amplitude only for Condition S_3 (280 Td·s; $t[47] = 3.84$, $p < .001$, $d = 1.10$, 95% CI [.50, 1.70]), with the schizophrenia group demonstrating reduced a-wave amplitudes relative to controls (see Figure 6). The groups also differed significantly in regression coefficients (slopes) across the 3 conditions of increasing luminance, $t(47) = 4.34$, $p < .001$, $d = 1.24$, 95% CI [.63, 1.85], with the schizophrenia group demonstrating a flatter slope across conditions ($M = -15.92$, $SD = 5.92$) than the control group ($M = -23.43$, $SD = 6.19$).

Finally, for scotopic b-wave amplitude there were significant main effects of stimulus condition ($p < .001$, $\eta_p^2 = .47$) and group ($p = .002$, $\eta_p^2 = .18$) and a significant Group × Condition interaction, $F(1.56,73.23) = 3.57$, $p = .044$, $\eta_p^2 = .071$. Post hoc comparisons revealed a significant difference between groups in b-wave amplitude for Conditions S_2 (28 Td·s; $t[47] = -3.88$, $p < .001$, $d = 1.11$, 95% CI [.51, 1.71]) and S_3, $t(47) = -2.93$, $p = .005$, $d = .84$, 95% CI [.25, 1.42], with the schizophrenia group ($n = 24$) demonstrating reduced amplitudes in both cases (see Figure 7). There was a trend-level difference between groups in slope of b-wave peak amplitudes across the three scotopic conditions, $t(47) = -1.78$, $p = .085$, $d = .51$, 95% CI [–.06, 1.08].

ERG Implicit Time

Photopic conditions. For a-wave implicit time, there was a significant main effect of stimulus condition ($p < .001$, $\eta_p^2 = .70$) and a significant Group × Condition interaction, $F(1.65,78.97) = 3.39$, $p = .047$, $\eta_p^2 = .07$, but the main effect of group was not significant, and the groups did not differ significantly in any of the conditions. For b-wave implicit time, there were significant main effects of stimulus condition ($p < .001$, $\eta_p^2 = .865$) and group ($p = .009$, $\eta_p^2 = .133$), but the interaction was not significant ($p > .05$). There was a significant difference between groups in b-wave implicit time for Condition P_2, $t(47.93) = 2.57$, $p = .013$; $d = .73$, 95% CI [.15, 1.30], with the schizophrenia group demonstrating longer latencies. No other post hoc comparisons were significant.

Scotopic conditions. In the mixed-model ANOVA examining implicit time during scotopic conditions there were no significant effects of group or Group × Condition interactions for either the

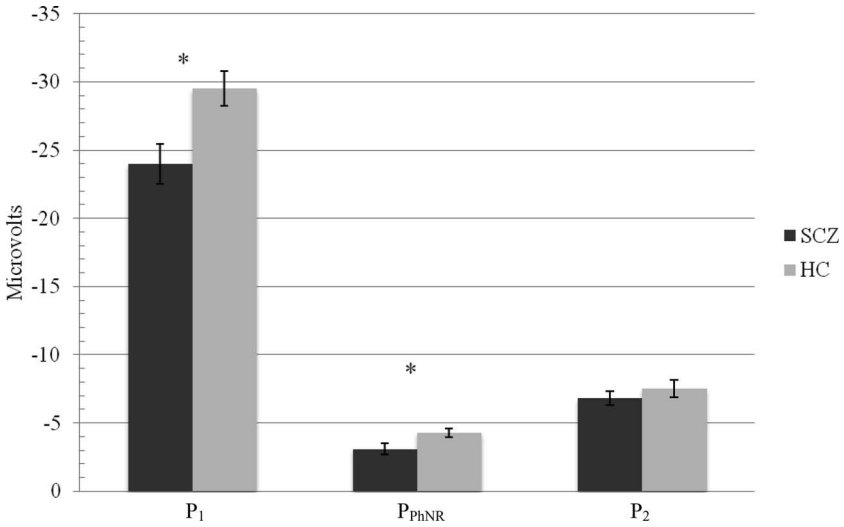

Figure 4. a-wave amplitude during photopic conditions. There was a significant difference between groups in photopic a-wave amplitude for the 100 Td·s at 1 Hz, unlit background condition (P_1; $t(48) = 2.86$, $p = .006$, $d = .81$, CI [.23, 1.39]) and 58 Td·s red at 3.4 Hz, blue background condition (P_{PhNR}; $t(48) = 2.33$, $p = .024$, $d = .66$, CI [.09, 1.23]), with the schizophrenia group demonstrating reduced photopic a-wave amplitudes as compared to the control group. There was no significant difference between groups in a-wave amplitude during the 100 Td·s at 2 Hz, 340 Td background condition (P_2; $^* p > .03$). Error bars represent standard errors.

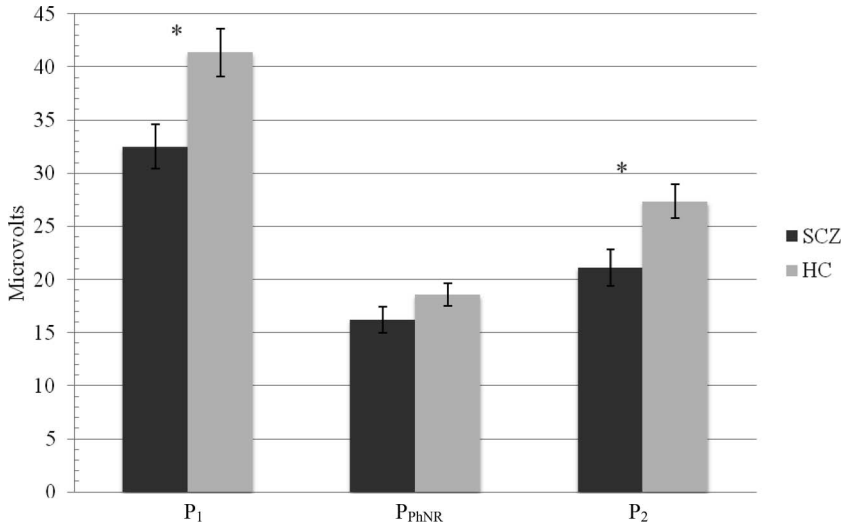

Figure 5. b-wave amplitude during photopic conditions. There was a significant difference between groups in photopic b-wave amplitude for the 100 Td·s at 1 Hz, unlit background condition (P_1; $t(48) = -2.92$, $p = .005$, $d = .83$, CI [.25, 1.40]) and 100 Td·s at 2 Hz, 340 Td background condition (P_2; $t(48) = -2.69$, $p = .010$, $d = .76$, CI [.19, 1.33]), with the schizophrenia group demonstrating reduced photopic b-wave amplitudes as compared to the control group. There was no significant difference between groups in b-wave amplitude during the 58 Td·s red at 3.4 Hz, blue background condition (P_{PhNR}; * $p > .0\bar{3}$). Error bars represent standard errors.

a-wave or b-wave data. There was a significant main effect of condition for both a-wave ($p < .001$, $\eta_p^2 = .838$) and b-wave ($p < .001$, $\eta_p^2 = .525$) implicit time, with implicit times being longer for less intense stimuli in both groups.

Flicker Test

There was a significant difference between groups in amplitude, $t(48) = -3.58$, $p = .001$, $d = 1.01$, 95% CI [.46, 1.60], with the schizophrenia group demonstrating reduced amplitudes relative to the control group. The groups were not significantly different in implicit time.

Photopic Negative Response

The schizophrenia group demonstrated attenuated negativity of the PhNR at 72 ms poststimulus: $t(48) = 2.39$, $p = .021$, $d = .68$, 95% CI [.11, 1.25]. On the variable of minimum PhNR, the degree of

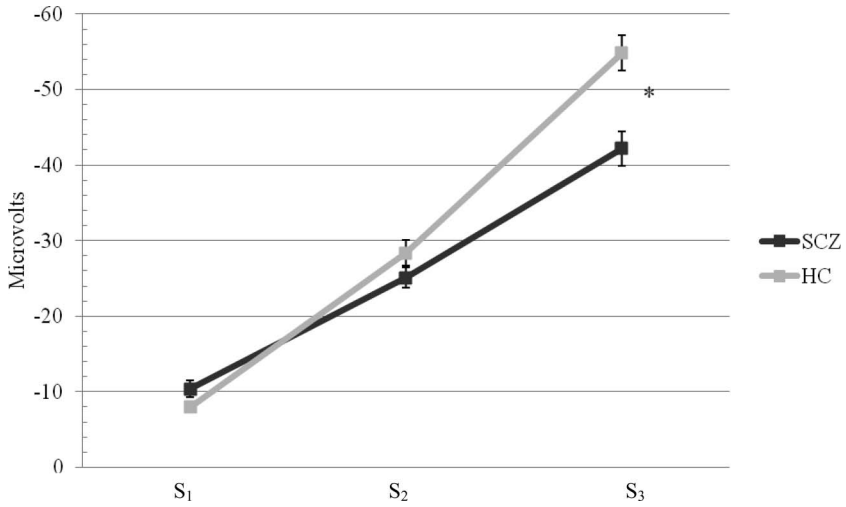

Figure 6. a-wave amplitude during scotopic conditions. There was a significant group difference in scotopic a-wave amplitude for the 280 Td·s condition (S_3; $t(47) = 3.84$, $p < .001$, $d = 1.10$, CI [.50, 1.70]) with the schizophrenia group demonstrating reduced b-wave amplitudes compared to the control group. However, there was no significant difference between groups in a-wave amplitude during the 2.8 Td·s (S_1) or 28 Td·s (S_2) conditions (* $p > .0\bar{3}$). Error bars represent standard errors.

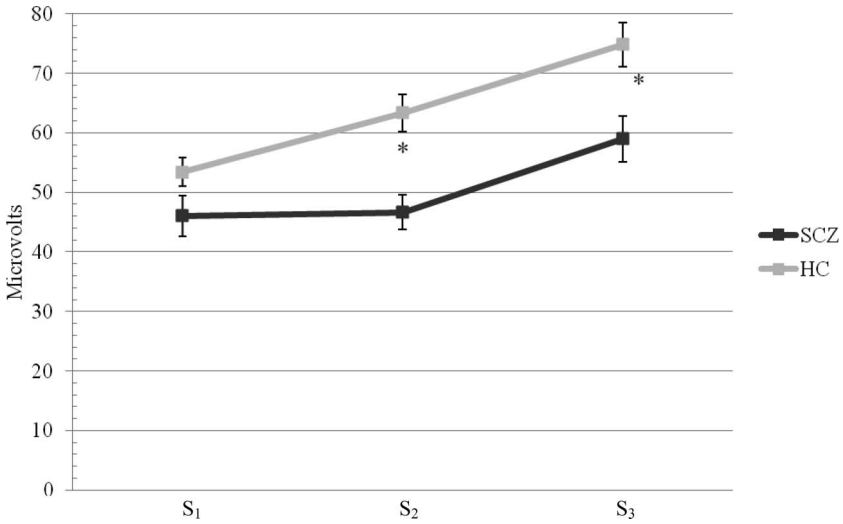

Figure 7. b-wave amplitude during scotopic conditions. There was a significant difference between groups in scotopic b-wave amplitude for the 28 Td·s condition (S_2; $t(47) = -3.88$, $p < .001$, $d = 1.11$, CI [.51, 1.71]) and the 280 Td·s condition (S_3; $t(47) = -2.93$, $p = .005$, $d = .84$, CI [.25, 1.42]) with the schizophrenia group demonstrating reduced scotopic b-wave amplitudes as compared to the control group. There was no significant difference between groups in b-wave amplitude during the 2.8 Td·s condition (S_1; $^{*}p > .0\bar{3}$). Error bars represent standard errors.

schizophrenia-related attenuation relative to controls approached significance: $t(48) = 1.77$, $p = .083$, $d = .50$, 95% CI [–.06, 1.06].

Baseline Pupil Diameter and Pupillary Response

In most stimulus conditions (P_1, P_{PhNR}, P_F, S_1, S_2, S_3) the average pupil diameter prior to the initial stimulus presentation was significantly smaller in the patient sample (*p*s = .002, .030, .01, .004, .01, and .03, respectively), and in the other stimulus condition (P_2), there was a similar trend ($p = .051$). However, the degree of increase in pupil size in response to light stimulation (expressed as percentage increase over the baseline pupil size after stimulus presentation) did not differ between groups. This suggests that both groups were responding to the same degree—in terms of extent of pupil size increase—to stimulus onsets. Although this also means that the schizophrenia group had small pupil sizes at baseline and after stimulus presentation, this could not account for group differences in fERG amplitudes and latencies, because the intensity of the light stimuli was continuously adjusted, based on pupil size, to ensure constant retinal illuminance in each condition (see the Method section; Davis et al., 2017).

Correlations With Symptom Dimensions and Medication Dose

The PANSS five-factor negative symptom dimension yielded large, significant correlations with a-wave amplitude during photopic conditions (P_{PhNR}; $r = .62$, $p = .001$) and with b-wave amplitude during scotopic conditions (S_1; $r = -.57$, $p = .004$) and correlated with a-wave implicit time during scotopic conditions to a lesser extent (S_1; $r = .45$, $p = .027$). An increase in negative symptoms was also correlated with an attenuated (i.e., less negative) minimum PhNR amplitude ($r = .40$, $p = .047$) and PhNR amplitude when measured at 72 ms poststimulus ($r = .44$, $p = .029$). The PANSS excitement symptom dimension was significantly correlated with b-wave implicit time during one scotopic conditions (S_2; $r = .76$, $p < .001$). No other correlations were significant. When an FDR correction was applied to the correlational analyses between fERG indices (amplitudes and implicit times) and the five symptom factors, however, only two of the correlations remained significant: negative symptoms and a-wave amplitude during photopic conditions (P_{PhNR}; FDR corrected $p = .029$) and excitement symptoms and b-wave implicit time during scotopic conditions (S_2; FDR corrected $p = .014$). There were no significant correlations between chlorpromazine equivalent dosage and photopic or scotopic fERG amplitudes or implicit times ($p > .05$ uncorrected in all cases; *r*s = .01–.36).

Discussion

The primary goal of this study was to refine our understanding of the nature and meaning of retinal dysfunction in schizophrenia. To achieve this, we (1) tested the same patients under both photopic and scotopic conditions; (2) used Troland-based stimulation, which ensured constant retinal illuminance in each condition, regardless of baseline pupil size or degree of change in pupil size in response to light stimulation; (3) sampled patients with a wide range of symptomatology; (4) excluded patients with medical conditions known to affect retinal health; (5) examined cone response to a flickering stimulus, and the PhNR of the retinal ganglion cells for the first time in a fERG study of schizophrenia; and (6) explored the relationships between fERG changes and symptom dimensions in schizophrenia. Importantly, all of these issues were examined using a portable ERG device, whose use could greatly increase feasibility of data collection in standard psychiatric clinical and research environments.

Data from photopic conditions suggest weakened cone and bipolar cell activity in schizophrenia. This effect was observed for both photoreceptors and bipolar cells when the difference between the background illuminance and stimulus flash intensity was large and when the stimulus was presented for a longer duration (e.g., 1 Hz vs. 2 Hz). However, even with less intense contrast between the stimulus and background, we observed amplitude reductions in photoreceptors or bipolar cells (but never both in any one of these weaker intensity conditions). Of note, the finding that schizophrenia-control differences are most observable when processing more intense stimuli is consistent with findings from other electrophysiological studies of schizophrenia (e.g., of mismatch negativity), and may indicate a reduced dynamic range within which the central nervous system can represent the environment (Todd, Michie, Schall, Ward, & Catts, 2012).

The finding of reduced representational range was observed most clearly, however, under scotopic conditions, where flash intensity increased from 2.8 to 280 Td·s by a factor of 10 across three conditions. As predicted, a-wave and b-wave amplitudes increased linearly, for both groups, with increases in stimulus intensity. However, as intensity increased, the schizophrenia group failed to demonstrate a similar increase in rod response to the control group, suggesting reduced response gain. The same pattern was observed for scotopic b-wave amplitude (bipolar cell) data, although to a lesser extent. Overall, these findings replicate data from prior studies, and show that retinal anomalies in schizophrenia occur in both light- and dark adapted conditions in the same patients, across a range of lighting and stimulus intensity conditions, and in patients without comorbid medical conditions that could confound findings. Importantly, however, the hypothesis regarding fERG detecting a compression of representational range in schizophrenia needs to be further explored using a larger number of light intensity conditions.

The findings of a between-groups difference in the PhNR when measured as negativity at 72 ms, and a trend-level between-groups difference in the overall PhNR minimum values, are intriguing, given that the stimuli that generated them also generated reduced a-wave activity but not b-wave activity. This suggests that while reduced signaling may characterize retinal ganglion cell activity in schizophrenia, this is not likely due to weakened input from bipolar cells, and may be due to neurotransmitter changes at the ganglion cell level (see the following text). An important question for future research is whether ganglion cell activity, which provides the primary feedforward input to the lateral geniculate nucleus of the thalamus, is related to reduced VEP amplitudes at V1, as weakened VEPs have been reported in many schizophrenia studies (Butler et al., 2007; González-Hernández et al., 2015).

An exploratory aim of the study was to examine relationships between fERG data and symptoms in the patient group. In a prior study, in a sample of acutely psychotic schizophrenia patients, Balogh et al. (2008) observed a negative correlation between PANSS positive symptoms and cone activity that was not observed after eight weeks of treatment. As in Balogh et al.'s posttreatment data, we did not observe a significant correlation with positive symptoms, which may be due to our schizophrenia sample consisting mainly (80%) of patients from post-inpatient levels of care. However, we observed five statistically significant correlations (when uncorrected for multiple comparisons) between attenuated retinal responsiveness and negative symptoms, which were most pronounced for amplitudes and implicit times in response to the least intense stimuli. These data suggest that reduced retinal activity may be a manifestation of the same neurotransmitter disturbance(s) leading to aspects of reduced behavioral activation subsumed under the category of negative symptoms. After FDR correction, however, only one of the findings with negative symptoms was significant. Therefore, important questions for future research are whether our correlational findings can be replicated, and whether changes in ERG amplitudes covary significantly with changes in negative symptoms over time. If both of these are found, it could suggest that reduced ERG amplitudes reflect (1) reduced retinal dopamine, since all retinal cell types have dopamine receptors, and reduced dopamine in the mesocortical pathway projecting to the prefrontal cortex is a proposed pathophysiology for negative symptoms (Abi-Dargham & Moore, 2003); (2) reduced retinal and cortical glutamate, as glutamate is the primary neurotransmitter used to convey photoreceptor signals forward in the visual system, and reduced cortical glutamate results in insufficient dopamine reaching prefrontal cortex regions (Citrome, 2014; Stahl, 2013); and/or (3) abnormalities in other neurotransmitter systems that have been observed in the brain in schizophrenia and that are involved in retinal function, such as GABA, glycine, serotonin, acetylcholine, nitric oxide, and BDNF (reviewed in Yang & Tsai, 2017 and Zrenner, 2006). In particular, interneurons such as horizontal cells are strongly GABA-ergic and changes in horizontal cell signaling could affect both photoreceptor and bipolar cell output (i.e., a-wave and b-wave characteristics). Interestingly, although all except one of the correlations with negative symptoms occurred with ERG indices on which patients and controls did not differ in amplitude or implicit time, the relationships may still reflect shared variance between variables that is unique to schizophrenia. As another recent example of this, whereas schizophrenia patients did not differ from people with bipolar disorder or healthy controls on several structural measures of the left and right optic radiations, optic radiation volume correlated with masking thresholds in a backward masking task for the schizophrenia group only (Reavis et al., 2017).

It is important to note several limitations of this study. One is that participants underwent a somewhat brief dark adaptation period prior to scotopic test administration (10 min) as compared to the ISCEV standard for optimizing rod functioning (20 min; Marmor et al., 2009). This practice may have resulted in a less-than-desired rod photoreceptor response and a greater than expected contribution of cones during scotopic tests. Though the use of a 10 min as opposed to a standard 20 min adaptation period has been shown to lead to only slight activity reductions (Hamilton & Graham, 2016), we cannot be certain that our findings would have been identical if a 20 min dark adaptation period was used. In fact, if rod abnormalities are indeed characteristic of schizophrenia, a full 20-min dark adaptation period might have led to larger between group differences than those we observed. On the other hand, the effect sizes we observed were similar to those reported in past studies using a longer dark adaptation period (e.g., Hébert et al., 2017), which suggests that the effects are robust to varying amounts of dark adaptation between 10 min and 20 min. Similarly, our most intense scotopic test condition (280 Td·s) may have stimulated both rod and cone photoreceptors, generating a mixed rod-cone ERG response rather than reflecting pure rod activity. Nevertheless, results of our scotopic tests support previous find-

ings of reduced a- and b-wave amplitudes in schizophrenia (Hébert et al., 2015; Warner et al., 1999).

A second limitation is the use of skin electrodes, as opposed to corneal contact or Dawson, Trick, and Litzkow (Dawson, Trick, & Litzkow, 1979) electrodes that have been used in past studies. Although skin electrodes offer an advantage of greater comfort, the ERG signals produced are generally smaller in amplitude, noisier, and more variable than those from direct contact methods (Heckenlively & Arden, 2006). A way to minimize noise and variability effects with skin electrodes is to average results over repeated trials in each condition (Creel, 2015), which is a feature of all RETeval protocols. Because our study results are consistent with findings from past studies demonstrating reduced a-wave and b-wave amplitudes, this suggests that the RETeval device, when used with skin electrodes, is sensitive enough to detect group differences. However, the possibility remains that some between group effects might have been larger if we had used more traditional electrode methods, even though this does risk greater potential data loss due to subjects not wishing to undergo testing using those methods.

Third, although both groups were matched on age, given known age-related decreases in retinal cell functioning (Lin, Tsubota, & Apte, 2016) these findings should be replicated in a younger sample in order to rule out the possibility of an effect of age on these results. Additionally, our interpretation that the increasing extent of schizophrenia-control differences as a function of light intensity reflects a reduced dynamic range of retinal signaling in schizophrenia is a post hoc explanation. Therefore, replication of this effect, across a wider range of stimulus intensities, is necessary in order to confirm this hypothesis. Furthermore, in this study the relationship between negative symptoms and attenuated retinal activity was observed using the PANSS, which is an established but older measure that has been criticized for not reflecting the current understanding of negative symptoms in terms of their multidimensionality, and for inadequate coverage of the construct (Blanchard & Cohen, 2006; Kumari, Malik, Florival, Manalai, & Sonje, 2017). Newer instruments such as the Clinical Assessment Interview for Negative Symptoms (Horan, Kring, Gur, Reise, & Blanchard, 2011; Kring, Gur, Blanchard, Horan, & Reise, 2013) and the Brief Negative Symptom Scale (Kirkpatrick et al., 2011) are thought to be more valid measures of negative symptoms, and it is possible that use of one of these scales may have led to different results.

A final limitation is that although this study examined retinal functioning under a range of light stimuli and lighting conditions, to replicate promising findings from past studies, the parameters chosen in this study may not have been sufficient to capture the full scope of retinal impairment in schizophrenia and so additional parameters should be explored in future research. For example, to adequately assess the hypothesis that photoreceptor and bipolar cell response gain is attenuated in schizophrenia, multiple conditions that differ only in light intensity (i.e., not in color or temporal frequency) need to be tested within the same session under both scotopic and photopic conditions. Furthermore, in an effort to balance using ISCEV standard tests, as well as other tests that may be relevant to schizophrenia, we chose stimulus parameters in some cases that were similar to tests from past studies, but are not ISCEV standard tests. However, several of the stimulus parameters used in prior fERG studies in schizophrenia were not reexamined in this study and perhaps, if combined with the current protocol, would provide superior between-groups discrimination. Future research in this area should aim toward creating a unified protocol for use in studies of schizophrenia. However, given the limited number of fERG studies of the disorder conducted to date, further exploration of retinal cell functioning in a wider range of conditions is needed before an optimally discriminating standardized protocol can be finalized.

In conclusion, we identified multiple stimulus conditions in the flash ERG that reliably discriminated between people with schizophrenia and psychiatrically healthy controls. This includes demonstrating the utility of a flicker stimulus for isolating cone-related activity, and the use of the PhNR for isolating retinal ganglion cell activity. We also demonstrated that the results appear to be independent of medication effects. Finally, we demonstrated that these findings can be obtained using a portable ERG device whose use does not require pupil dilation or the use of corneal contact electrodes, and where each stimulus condition can be typically completed in 1-2 min. This highlights the feasibility of ERG testing in routine clinical practice, something that may become important should future data confirm the status of ERG indices as biomarkers of schizophrenia, specific symptom clusters, risk status, and/or treatment-related changes.

References

Abi-Dargham, A., & Moore, H. (2003). Prefrontal DA transmission at D1 receptors and the pathology of schizophrenia. *The Neuroscientist, 9,* 404–416. http://dx.doi.org/10.1177/1073858403252674

American Clinical Neurophysiology Society. (2006). Guideline 9B: Guidelines on visual evoked potentials. *Journal of Clinical Neurophysiology: Official Publication of the American Electroencephalographic Society, 23,* 138–156. http://dx.doi.org/10.1097/00004691-200604000-00011

Balogh, Z., Benedek, G., & Kéri, S. (2008). Retinal dysfunctions in schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 32,* 297–300. http://dx.doi.org/10.1016/j.pnpbp.2007.08.024

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society Series B. Methodological, 57,* 289–300.

Blanchard, J. J., & Cohen, A. S. (2006). The structure of negative symptoms within schizophrenia: Implications for assessment. *Schizophrenia Bulletin, 32,* 238–245. http://dx.doi.org/10.1093/schbul/sbj013

Blokhuis, C., Demirkaya, N., Cohen, S., Wit, F. W. N. M., Scherpbier, H. J., Reiss, P., . . . Pajkrt, D. (2016). The eye as a window to the brain: Neuroretinal thickness is associated with microstructural white matter injury in HIV-infected children. *Investigative Ophthalmology & Visual Science, 57,* 3864–3871. http://dx.doi.org/10.1167/iovs.16-19716

Bresnick, G. H., & Palta, M. (1987). Temporal aspects of the electroretinogram in diabetic retinopathy. *Archives of Ophthalmology, 105,* 660–664. http://dx.doi.org/10.1001/archopht.1987.01060050078042

Burguera, J. A., Vilela, C., Traba, A., Ameave, Y., & Vallet, M. (1990). The electroretinogram and visual evoked potentials in patients with Parkinson's disease. *Archivos de Neurobiología, 53,* 1–7.

Butler, P. D., Martinez, A., Foxe, J. J., Kim, D., Zemon, V., Silipo, G., . . . Javitt, D. C. (2007). Subcortical visual dysfunction in schizophrenia drives secondary cortical impairments. *Brain: A Journal of Neurology, 130*(Part 2), 417–430. http://dx.doi.org/10.1093/brain/awl233

Chu, E. M-Y., Kolappan, M., Barnes, T. R. E., Joyce, E. M., & Ron, M. A. (2012). A window into the brain: An in vivo study of the retina in schizophrenia using optical coherence tomography. *Psychiatry Research: Neuroimaging, 203,* 89–94. http://dx.doi.org/10.1016/j.pscychresns.2011.08.011

Citrome, L. (2014). Unmet needs in the treatment of schizophrenia: New targets to help different symptom domains. *The Journal of Clinical Psychiatry, 75*(Suppl. 1), 21–26. http://dx.doi.org/10.4088/JCP.13049su1c.04

Creel, D. (2015). *The electroretinogram and electro-oculogram: Clinical applications*. Retrieved from http://webvision.med.utah.edu/book/electrophysiology/the-electroretinogram-clinical-applications/

Davis, C. Q., Kraszewska, O., & Manning, C. (2017). Constant luminance (cd · s/m^2) versus constant retinal illuminance (Td·s) stimulation in flicker ERGs. *Documenta Ophthalmologica, 134,* 75–87. http://dx.doi.org/10.1007/s10633-017-9572-3

Dawson, W. W., Trick, G. L., & Litzkow, C. A. (1979). Improved electrode for electroretinography. *Investigative Ophthalmology & Visual Science, 18,* 988–991.

Dhillon, B., & Dhillon, N. (2008). The retina as a window to the brain. *Archives of Neurology, 65,* 1547–1548. http://dx.doi.org/10.1001/archneur.65.11.1547

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. (2002, November). *Structured Clinical Interview for DSM–IV–TR Axis I Disorders, Research Version, Patient Edition*. New York, NY: Biometrics Research, New York State Psychiatric Institute.

First, M. B., Spitzer, R. L., Williams, J. B., & Gibbon, M. (2002, November). *Structured Clinical Interview for DSM–IV–TR Axis I Disorders, Research Version, Non-Patient Edition*. New York, NY: Biometrics Research, New York State Psychiatric Institute.

Frohman, E. M., Fujimoto, J. G., Frohman, T. C., Calabresi, P. A., Cutter, G., & Balcer, L. J. (2008). Optical coherence tomography: A window into the mechanisms of multiple sclerosis. *Nature Reviews Neurology, 4,* 664–675. http://dx.doi.org/10.1038/ncpneuro0950

González-Hernández, J. A., Pita-Alcorta, C., Wolters, C. H., Padrón, A., Finalé, A., Galán-García, L., . . . Lencer, R. (2015). Specificity and sensitivity of visual evoked potentials in the diagnosis of schizophrenia: Rethinking VEPs. *Schizophrenia Research, 166*(1–3), 231–234. http://dx.doi.org/10.1016/j.schres.2015.05.007

Hamilton, R., & Graham, K. (2016). Effect of shorter dark adaptation on ISCEV standard DA 0.01 and DA 3 skin ERGs in healthy adults. *Documenta Ophthalmologica, 133,* 11–19. http://dx.doi.org/10.1007/s10633-016-9554-x

Hayes, R. D., & Merigan, W. H. (2007). Mechanisms of sensitivity loss due to visual cortex lesions in humans and macaques. *Cerebral Cortex, 17,* 1117–1128. http://dx.doi.org/10.1093/cercor/bhl021

Hébert, M., Gagné, A.-M., Paradis, M.-E., Jomphe, V., Roy, M.-A., Mérette, C., & Maziade, M. (2010). Retinal response to light in young nonaffected offspring at high genetic risk of neuropsychiatric brain disorders. *Biological Psychiatry, 67,* 270–274. http://dx.doi.org/10.1016/j.biopsych.2009.08.016

Hébert, M., Mérette, C., Paccalet, T., Émond, C., Gagné, A.-M., Sasseville, A., & Maziade, M. (2015). Light evoked potentials measured by electroretinogram may tap into the neurodevelopmental roots of schizophrenia. *Schizophrenia Research, 162*(1–3), 294–295. http://dx.doi.org/10.1016/j.schres.2014.12.030

Hébert, M., Mérette, C., Paccalet, T., Gagné, A.-M., & Maziade, M. (2017). Electroretinographic anomalies in medicated and drug free patients with major depression: Tagging the developmental roots of major psychiatric disorders. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 75,* 10–15. http://dx.doi.org/10.1016/j.pnpbp.2016.12.002

Heckenlively, J. R., & Arden, G. B. (Eds.). (2006). *Principles and practice of clinical electrophysiology of vision* (2nd ed.). Cambridge, MA: MIT Press.

Horan, W. P., Kring, A. M., Gur, R. E., Reise, S. P., & Blanchard, J. J. (2011). Development and psychometric validation of the Clinical Assessment Interview for Negative Symptoms (CAINS). *Schizophrenia Research, 132*(2–3), 140–145. http://dx.doi.org/10.1016/j.schres.2011.06.030

Hyett, M., & Parker, G. (2013). Loss of light in the eyes: A window to melancholia. *Medical Hypotheses, 81,* 186–191. http://dx.doi.org/10.1016/j.mehy.2013.05.008

Jindal, V. (2015). Interconnection between brain and retinal neurodegenerations. *Molecular Neurobiology, 51,* 885–892. http://dx.doi.org/10.1007/s12035-014-8733-6

Kato, K., Kondo, M., Sugimoto, M., Ikesugi, K., & Matsubara, H. (2015). Effect of pupil size on flicker ERGs recorded with RETeval System: New mydriasis-free full-field ERG system. *Investigative Ophthalmology & Visual Science, 56,* 3684–3690. http://dx.doi.org/10.1167/iovs.14-16349

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin, 13,* 261–276. http://dx.doi.org/10.1093/schbul/13.2.261

Kay, S. R., & Sevy, S. (1990). Pyramidical model of schizophrenia. *Schizophrenia Bulletin, 16,* 537–545. http://dx.doi.org/10.1093/schbul/16.3.537

Kirkpatrick, B., Strauss, G. P., Nguyen, L., Fischer, B. A., Daniel, D. G., Cienfuegos, A., & Marder, S. R. (2011). The brief negative symptom scale: Psychometric properties. *Schizophrenia Bulletin, 37,* 300–305. http://dx.doi.org/10.1093/schbul/sbq059

Kizawa, J., Machida, S., Kobayashi, T., Gotoh, Y., & Kurosaka, D. (2006). Changes of oscillatory potentials and photopic negative response in patients with early diabetic retinopathy. *Japanese Journal of Ophthalmology, 50,* 367–373. http://dx.doi.org/10.1007/s10384-006-0326-0

Kring, A. M., Gur, R. E., Blanchard, J. J., Horan, W. P., & Reise, S. P. (2013). The Clinical Assessment Interview for Negative Symptoms (CAINS): Final development and validation. *The American Journal of Psychiatry, 170,* 165–172. http://dx.doi.org/10.1176/appi.ajp.2012.12010109

Kumari, S., Malik, M., Florival, C., Manalai, P., & Sonje, S. (2017). *An assessment of five (PANSS, SAPS, SANS, NSA-16, CGI-SCH) commonly used symptoms rating scales in schizophrenia and comparison to newer scales (CAINS, BNSS)*. Retrieved from http://dx.doi.org/10.4172/2155-6105.1000324

Lavoie, J., Maziade, M., & Hébert, M. (2014). The brain through the retina: The flash electroretinogram as a tool to investigate psychiatric disorders. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 48,* 129–134. http://dx.doi.org/10.1016/j.pnpbp.2013.09.020

Lavoie, M.-P., Lam, R. W., Bouchard, G., Sasseville, A., Charron, M.-C., Gagné, A.-M., . . . Hébert, M. (2009). Evidence of a biological effect of light therapy on the retina of patients with seasonal affective disorder. *Biological Psychiatry, 66,* 253–258. http://dx.doi.org/10.1016/j.biopsych.2008.11.020

Lin, J. B., Tsubota, K., & Apte, R. S. (2016). A glimpse at the aging eye. *NPJ Aging and Mechanisms of Disease, 2,* 16003. http://dx.doi.org/10.1038/npjamd.2016.3

Lindenmayer, J.-P., Bernstein-Hyman, R., Grochowski, S., & Bark, N. (1995). Psychopathology of Schizophrenia: Initial validation of a 5-factor model. *Psychopathology, 28,* 22–31. http://dx.doi.org/10.1159/000284896

London, A., Benhar, I., & Schwartz, M. (2013). The retina as a window to the brain-from eye research to CNS disorders. *Nature Reviews Neurology, 9,* 44–53. http://dx.doi.org/10.1038/nrneurol.2012.227

Machida, S. (2012). Clinical applications of the photopic negative response to optic nerve and retinal diseases. *Journal of Ophthalmology, 2012,* 397178. http://dx.doi.org/10.1155/2012/397178

Marmor, M. F., Fulton, A. B., Holder, G. E., Miyake, Y., Brigell, M., & Bach, M., & the International Society for Clinical Electrophysiology of Vision. (2009). ISCEV Standard for full-field clinical electroretinography (2008 update). *Documenta Ophthalmologica, 118,* 69–77. http://dx.doi.org/10.1007/s10633-008-9155-4

McCulloch, D. L., Marmor, M. F., Brigell, M. G., Hamilton, R., Holder, G. E., Tzekov, R., & Bach, M. (2015). ISCEV Standard for full-field clinical electroretinography (2015 update). *Documenta Ophthalmologica, 130,* 1–12. http://dx.doi.org/10.1007/s10633-014-9473-7

Msall, M. E. (2006). The retina as a window to the brain in vulnerable neonates. *Pediatrics, 117,* 2287–2289. http://dx.doi.org/10.1542/peds.2006-0385

Nowacka, B., Lubiński, W., Honczarenko, K., Potemkowski, A., & Safranow, K. (2015). Bioelectrical function and structural assessment of the retina in patients with early stages of Parkinson's disease (PD). *Documenta Ophthalmologica, 131,* 95–104. http://dx.doi.org/10.1007/s10633-015-9503-0

Pescosolido, N., Fazio, S., & Rusciano, D. (2014). Reliability of the implicit time of flicker erg b-wave as an objective diagnostic tool for retinopathies. *JSM Biotechnology & Biomedical Engineering, 2,* 1037.

Realmuto, G., Purple, R., Knobloch, W., & Ritvo, E. (1989). Electroretinograms (ERGs) in four autistic probands and six first-degree relatives. *Canadian Journal of Psychiatry, 34,* 435–439. http://dx.doi.org/10.1177/070674378903400513

Reavis, E. A., Lee, J., Wynn, J. K., Narr, K. L., Njau, S. N., Engel, S. A., & Green, M. F. (2017). Linking optic radiation volume to visual perception in schizophrenia and bipolar disorder. *Schizophrenia Research, 190*(Suppl. C), 102–106. http://dx.doi.org/10.1016/j.schres.2017.03.027

Roth, S. (2015). Inhaled anesthesia, apoptosis, and the developing retina: A window into the brain? *Anesthesia and Analgesia, 121,* 1117–1118. http://dx.doi.org/10.1213/ANE.0000000000000937

Schönfeldt-Lecuona, C., Kregel, T., Schmidt, A., Pinkhardt, E. H., Lauda, F., Kassubek, J., . . . Gahr, M. (2016). From imaging the brain to imaging the retina: Optical coherence tomography (OCT) in schizophrenia. *Schizophrenia Bulletin, 42,* 9–14.

Silverstein, S. M. (2016). Visual Perception Disturbances in Schizophrenia: A Unified Model. *Nebraska Symposium on Motivation, 63,* 77–132. http://dx.doi.org/10.1007/978-3-319-30596-7_4

Silverstein, S. M., Demmin, D. L., & Bednar, J. A. (2017). Computational modeling of contrast sensitivity and orientation tuning in first-episode and chronic schizophrenia. *Computational Psychiatry,* 1–30. http://dx.doi.org/10.1162/CPSY_a_00005

Silverstein, S. M., & Rosen, R. (2015). Schizophrenia and the eye. *Schizophrenia Research Cognition, 2,* 46–55. http://dx.doi.org/10.1016/j.scog.2015.03.004

Skottun, B. C., & Skoyles, J. R. (2007). Contrast sensitivity and magnocellular functioning in schizophrenia. *Vision Research, 47,* 2923–2933. http://dx.doi.org/10.1016/j.visres.2007.07.016

Stahl, S. M. (2013). *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications*. New York, NY: Cambridge University Press.

Tahara, K., Matsuura, T., & Otori, T. (1993). Diagnostic evaluation of diabetic retinopathy by 30-Hz flicker electroretinography. *Japanese Journal of Ophthalmology, 37,* 204–210.

Todd, J., Michie, P. T., Schall, U., Ward, P. B., & Catts, S. V. (2012). Mismatch negativity (MMN) reduction in schizophrenia-impaired prediction—Error generation, estimation or salience? *International Journal of Psychophysiology, 83,* 222–231. http://dx.doi.org/10.1016/j.ijpsycho.2011.10.003

Virsu, V., & Rovamo, J. (1979). Visual resolution, contrast sensitivity, and the cortical magnification factor. *Experimental Brain Research, 37,* 475–494. http://dx.doi.org/10.1007/BF00236818

Viswanathan, S., Frishman, L. J., Robson, J. G., Harwerth, R. S., & Smith, E. L., III. (1999). The photopic negative response of the macaque electroretinogram: Reduction by experimental glaucoma. *Investigative Ophthalmology & Visual Science, 40,* 1124–1136.

Warner, R., Laugharne, J., Peet, M., Brown, L., & Rogers, N. (1999). Retinal function as a marker for cell membrane omega-3 fatty acid depletion in schizophrenia: A pilot study. *Biological Psychiatry, 45,* 1138–1142. http://dx.doi.org/10.1016/S0006-3223(98)00379-5

Yang, A. C., & Tsai, S.-J. (2017). New targets for schizophrenia treatment beyond the dopamine hypothesis. *International Journal of Molecular Sciences, 18,* 1689. http://dx.doi.org/10.3390/ijms18081689

Young, B., Eggenberger, E., & Kaufman, D. (2012). Current electrophysiology in ophthalmology: A review. *Current Opinion in Ophthalmology, 23,* 497–505. http://dx.doi.org/10.1097/ICU.0b013e328359045e

Zrenner, E. (2006). Drug side effects and toxicology of the visual system. In J. R. Heckenlively & G. B. Arden (Eds.), *Principles and practice of clinical electrophysiology of vision* (2nd ed., pp. 655–663). Cambridge, MA: MIT Press.

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