Schizophrenia Research xxx (xxxx) xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

People with current major depression resemble healthy controls on flash Electroretinogram indices associated with impairment in people with stabilized schizophrenia

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ARTICLE INFO

Article history:
Received 28 March 2019
Received in revised form 10 July 2019
Accepted 13 July 2019
Available online xxxx

Keywords:
Electroretinography
ERG
Schizophrenia
Major depressive disorder
Retina

ABSTRACT

Flash electroretinography (fERG) has been used to identify anomalies in retinal functioning in several psychiatric disorders. In schizophrenia (SCZ), fERG abnormalities are reliably observed, but findings from studies of major depressive disorder (MDD) have been less consistent. In this study, fERG data were recorded from MDD patients in a current major depressive episode ($n = 25$), and compared to data from SCZ patients ($n = 25$) and healthy controls (HC; $n = 25$), to determine the degree to which fERG anomalies in acute MDD overlap or contrast with those observed in stabilized (though not symptom free) SCZ. The primary variables of interest were a-wave (photoreceptor activity), b-wave (bipolar-Müller cell activity), and photopic negative response (PhNR; ganglion cell activity) amplitudes and implicit times. Across most conditions, there were no significant differences between the MDD and HC groups in a- or b-wave response, but the SCZ group consistently demonstrated reduced amplitudes. Interestingly, MDD patients demonstrated an increase in photopic a-wave implicit time relative to SCZ patients, and a decrease in PhNR implicit time relative to controls. Correlations between BDI-II scores and fERG metrics were not significant for either patient group. Overall, these data indicate that, using an fERG protocol that distinguishes SCZ patients from controls, MDD patients experiencing a current depressive episode closely resemble healthy controls in their fERG responses. Therefore, MDD-related fERG changes may be more subtle than those observed in SCZ and detectable only with larger sample sizes than we employed and/or using a different set of fERG test parameters.

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1. Introduction

During fetal developmental, the retinae emerge from the same tissue as the brain and retain a direct connection with the brain via the optic nerve bundle, which includes both signals sent from the retina to the brain and inputs from the brain to the retina (Erskine and Herrera 2014; Ortiz et al. 2017). Thus, the retina is a part of the CNS and it can provide a useful model of broader neural dysfunction in psychiatric disorders (Lavoie et al. 2014; London et al. 2012).

Changes in visual function are a well-known feature of a number of neurological and psychiatric conditions, including Parkinson's disease (e.g., Nowacka et al. 2015; Weil et al. 2016), Alzheimer's disease (e.g., Valenti 2010), multiple sclerosis (e.g., Balcer et al., 2017), bipolar disorder (e.g., Fernandes et al. 2017), autism spectrum disorders (e.g., Bakroon and Lakshminarayanan 2016), and schizophrenia (e.g., Silverstein 2016). In schizophrenia, these visual disturbances involve impairments in perceptual organization (e.g., Silverstein and Keane 2011), contrast sensitivity (e.g., Shoshina and Shelepin 2015), spatial frequency processing (e.g., Kim et al. 2015), motion perception (e.g., Chen 2011), and color perception (e.g., Shuwairi et al. 2002), as well as various forms of visual distortions (e.g., Silverstein et al. 2017), among others (Silverstein 2016). Additionally, these changes have been associated with symptom severity, illness progression, disease stage, and clinical outcome (e.g., Rassovsky et al. 2011; Schubert et al. 2005; Silverstein and Keane 2011), underscoring their clinical significance and potential utility as an indicator of clinical state. Alterations

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https://doi.org/10.1016/j.schres.2019.07.024
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Please cite this article as: D.L. Demmin, R. Netser, M.W. Roché, et al., People with current major depression resemble healthy controls on flash Electroretinogram indices as..., Schizophrenia Research, https://doi.org/10.1016/j.schres.2019.07.024

in visual functioning have also been investigated in depressive disorders. In addition to experiences of diminished light and color perception that are commonly reported by patients with major depressive disorder (MDD) (Friberg and Borrero 2000), reduced contrast sensitivity (Bubl et al. 2010; Fam et al. 2013), enhanced motion perception (Golomb et al. 2009), and abnormalities in visual evoked potentials (VEPs) have been observed in MDD (Normann et al., 2007).

Flash electroretinography (fERG) is an increasingly popular methodology for examining retinal functioning in psychiatric disorders. fERG records electrical potentials of retinal cells in response to flashed or flickering unpatterned light stimuli. The activity of several cell groups give rise to the fERG waveform, which consists of two primary components: a negative a-wave indicative of photoreceptor cell hyperpolarization and a positive b-wave reflecting bipolar-Müller cell complex depolarization. fERG can be recorded under photopic (light-adapted) or scotopic (dark-adapted) conditions (Marmor et al. 2009). The photopic negative response (PhNR; Machida 2012; Viswanathan et al. 1999) is a third waveform component, reflecting the activity of retinal ganglion cells, that is observed following the b-wave under certain photopic test parameters. The amplitude and implicit time (i.e., response latency) of each fERG waveform component can be examined.

Abnormalities in retinal cell signaling in schizophrenia have been consistently demonstrated. In both photopic and scotopic conditions, a reduction in a-wave (Balogh et al. 2008; Demmin et al. 2018; Hébert et al. 2015; Warner et al. 1999) and b-wave (Demmin et al. 2018; Hébert et al. 2015; Warner et al. 1999) amplitudes has been observed. Attenuated response to a flicker stimulus, in which flash stimuli are presented at a sufficiently high frequency so as to isolate cone functioning (i.e., Young et al. 2012), has also been demonstrated in schizophrenia (Demmin et al. 2018). A more recent finding is an attenuation of the PhNR, reflecting reduced retinal ganglion cell activity in patients with schizophrenia, when compared to healthy controls (Demmin et al. 2018). Abnormalities in implicit time have been less frequently observed, however, some of the above-mentioned studies have reported an increase in photopic b-wave implicit time in schizophrenia patients in comparison to healthy controls (i.e., Demmin et al. 2018; Hébert et al. 2015). One prior study observed that photopic a-wave amplitude in schizophrenia patients upon hospital admission was significantly reduced, but then improved (although still without reaching normal levels), after eight weeks of treatment, suggesting a potential relationship with clinical state. However, a reduction in scotopic b-wave amplitude was observed in a nonaffected genetic high-risk youth sample, demonstrating that anomalies of the bipolar-Müller cells complex may be trait markers of disease susceptibility (Hébert et al. 2010).

Anomalies in retinal functioning have been observed in MDD, using both pattern (pERG) and fERG. The pERG is an electrophysiological measure of retinal response to visual pattern simulation that reflects ganglion cell function (Bach et al. 2013). Using pERG, Bubl et al. (2010) observed a reduction in retinal contrast gain in MDD patients experiencing a current episode of depression when compared to healthy controls. These reductions in retinal contrast processing have also been linked to depressive symptom severity (Bubl et al. 2010) and have been shown to normalize with remission (Bubl et al. 2012), suggesting a relationship with severity of depression. A number of studies have also examined retinal function in major depression using fERG, where anomalies in retinal cell signaling have been observed in several studies and, similarly, appear to be related to severity of depression. For example, in the largest study in MDD using fERG to date ($n = 100$ MDD patients), Hébert et al. (2017) reported increased photopic (cone) and scotopic (mixed rods/cones) b-wave implicit time and reduced scotopic (mixed rods/cones) a-wave and b-wave amplitudes in medicated patients, when compared to healthy controls. In a much smaller unmedicated subgroup of patients with MDD ($n = 17$) from the same study, similar scotopic effect sizes to those in the medicated group were observed; however, unique to the unmedicated group was a reduction in photopic a- and b-wave amplitudes at Vmax (the maximum amplitude at the saturation point of the luminance curve), suggesting a possible positive effect of medication on photopic ERG amplitudes in MDD. It could not be determined, however, whether the baseline differences in symptom severity between the unmedicated and medicated groups might have caused these ERG differences.

Both Hébert et al. (2004) and Lavoie et al. (2009) discovered a seasonal change in retinal sensitivity in patients with seasonal affective disorder (SAD) when compared to healthy controls, whereby patients demonstrated reduced rod sensitivity in winter months that, in one study, was normalized in summer months (Lavoie et al. 2009). Additionally, Lavoie and colleagues found that the degree of change in the patient group was associated with depressive symptom severity (Lavoie et al., 2014 in reference to Lavoie et al. 2009). This seasonal change in rod sensitivity was also observed in patients with subsyndromal (albeit distressing) SAD, when compared with healthy controls (Hébert et al. 2002). Similarly, an effect of depressive state on photopic retinal response in SAD has also been reported, whereby patients demonstrated reduced b-wave Vmax and increased b-wave implicit time during winter months that again normalized during summer months (symptom remission) (Lavoie et al. 2009). Together, these findings in SAD provide additional evidence of a state-related changes in retinal functioning in depressive disorders.

In contrast to the above findings, Fornaro et al. (2011) observed that baseline scotopic b-wave amplitudes and implicit time measurements were not significantly different between patients with MDD and healthy controls. However, in their MDD sample, b-wave amplitudes were significantly higher in patients who responded after 12 weeks of treatment with duloxetine when compared to non-responders. Furthermore, final responders showed a significant reduction (normalization) of scotopic b-wave amplitude (Fornaro et al. 2011), suggesting an effect of medication on scotopic ERG waveforms in the opposite direction to that reported in Hebert et al. (Hébert et al. 2017). Fountoulakis et al. (2005) also found no differences in photopic a-wave or b-wave amplitudes or latencies in patients with MDD relative to healthy controls, though they did report a positive correlation between depressive symptom severity and b-wave amplitude in the combined group (Fountoulakis et al. 2005). Lastly, in a study reporting reduced visual contrast sensitivity performance in MDD patients, there were no significant differences between the MDD and healthy control groups in scotopic a- or b-wave amplitudes or implicit time measurements (Fam et al. 2013) suggesting that abnormal contrast sensitivity in MDD was fully mediated by cortical processing impairments.

The literature reviewed above indicates that while ERG anomalies have been reliably demonstrated in a number of studies in schizophrenia, results from studies of MDD are less consistent. Moreover, some of the reported anomalies in retinal cell signaling in MDD patients parallel those that have been established in schizophrenia (e.g., Hébert et al. 2017), leading to questions of diagnostic specificity of these ERG anomalies. Therefore, in this study we directly compared the fERG performance of MDD patients experiencing a current major depressive episode to that of stabilized, but not symptom free, schizophrenia patients, and that of healthy controls, in order to clarify the extent of changes in acute MDD relative to both groups, thereby addressing both the issues of presence of MDD-related abnormality and diagnostic specificity.

2. Materials and methods

2.1. Participants

ERG data were recorded from 25 patients with schizophrenia (SCZ), 25 patients with major depressive disorder (either single episode or recurrent; MDD) in a current major depressive episode, and 25 healthy controls (HC; see Table 1).

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Table 1
Demographic Variables by Group.

	MDD ($N = 25$)	SCZ ($N = 25$)	HC ($N = 25$)
Variable	*n*(%)	*n*(%)	*n*(%)
Sex			
Female	11(44%)	4(16%)	7(28%)
Male	14(56%)	21(84%)	18(72%)
Age (Mean[SD])	32.33(14.87)	36.80(10.83)	32.60(11.91)
Range	18, 57	20, 58	18, 60
18–32	14(56%)	9(36%)	15(60%)
33–46	2(8%)	10(40%)	7(28%)
47–60	9(36%)	6(24%)	3(12%)
Parental Education (Mean[SD])	15.32(11.71)	12.30(2.96)	14.26(2.69)
Race			
Caucasian	15(60%)	13(52%)	14(56%)
African-American	5(20%)	7(28%)	7(28%)
Asian	5(20%)	5(20%)	3(12%)
Other	0(0%)	0(0%)	1(4%)
Ethnicity			
Hispanic	4(16%)	5(20%)	5(20%)

MDD = major depressive disorder, SCZ = schizophrenia, HC = healthy control.
All MDD patients and all but one SCZ patient was taking medication.

Patients were recruited from Rutgers University Behavioral Health Care's adult inpatient unit (SCZ: $n = 5$, MDD: $n = 23$), partial hospital programs (SCZ: $n = 16$, MDD: $n = 2$), and outpatient program (SCZ: $n = 4$). At the time of testing, all MDD patients and all but one SCZ patient were prescribed psychiatric medication. In the MDD group, 72% of patients ($n = 18$) had recurrent major depressive episodes and 28% ($n = 7$) met criteria for a single episode. All patients in the MDD group were experiencing a current major depressive episode (past month). No patients in the MDD group reported experiences of psychotic symptoms. Healthy control participants were recruited from the community. All participants were between the ages of 18 and 60 years old. In the HC and MDD groups, participants who reported a family history (first-degree relatives) of psychotic disorders were excluded from study participation. In all groups, participants with an active substance use disorder within the last six months, a history of ocular disease or injury, or medical conditions known to affect vision (e.g., diabetes, hypertension) were excluded from study participation.

2.2. Procedure

Patient diagnoses were confirmed using the Structured Clinical Interview for *DSM–IV* Axis I Disorders (SCID-IV; First, et al., 2002a). 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., 2002b). The Beck Depression Inventory-II (BDI-II; Beck et al. 1996) was administered to both patient groups in order to assess depressive symptom severity.

Interviews were conducted by trained research assistants and clinical diagnoses were reviewed and established in a weekly consensus meeting with clinical raters and two experienced research psychologists. The study was approved by the Rutgers Institutional Review Board (Pro20150002281), and written informed consent was obtained from each participant.

2.2.1. Apparatus

fERG data were collected using the RETeval, an FDA-approved portable ERG device (LKC Technologies, Gaithersburg, MD). fERG was recorded from each eye, at a sampling rate of 2 kHz, using an adhesive skin electrode containing positive, negative, and ground electrodes placed 2 mm below each lower eyelid. While the use of skin electrodes has been associated with increased noise and reduced amplitudes (Heckenlively and Arden 2006), they afford greater comfort than corneal contact or DTL electrodes, and thus are better tolerated. In addition, the issue of noise is largely eliminated through averaging signals over multiple trials (Creel 2015). Retinal illuminance was measured in Trolands, in which there is continuous measurement of pupil size and dynamic adjustment of light intensity to compensate for changes in pupil size, so that a constant amount of light is delivered to the retina on each trial within each condition (Davis et al. 2017; Kato et al. 2015).

2.2.2. ERG recording

Participants were light adapted for five minutes prior to photopic fERG recording, after spending several hours in lighted conditions prior to the start of the session. Photopic tests included: a 100 Td-s (~4 cd-s/m^2 [assuming a 6 mm pupil diameter]) flash stimulus presented at a 1 Hz repetition rate with no background luminance (P_1); a 58 Td-s (~2 cd-s/m^2 [assuming a 6 mm pupil diameter]) red stimulus presented at 3.4 Hz, with a 380 Td blue background (P_2); a 100 Td-s (~4 cd-s/m^2 [assuming a 6 mm pupil diameter]) flash stimulus presented at a 2 Hz repetition rate with a 340 Td background (P_3); and an 85 Td-s (~3 cd-s/m^2 [assuming a 6 mm pupil diameter]) flickering (at 28.3 Hz) stimulus (P_F). Participants were then dark adapted for 10 min before scotopic test administration. For scotopic tests, stimulus intensity increased by a factor of 10 for each trial, beginning with a 2.8 Td-s (~0.10 cd-s/m^2 [assuming a 6 mm pupil diameter]) flash stimulus presented at 0.25 Hz (S_1), then a 28 Td-s (~1 cd-s/m^2 [assuming a 6 mm pupil diameter]) flash stimulus presented at 0.1 Hz (S_2), and finally, a 280 Td-s (~10 cd-s/m^2 [assuming a 6 mm pupil diameter]) flash stimulus presented at 0.05 Hz (S_3).

fERG data were collected on patients with MDD as an addition to an ongoing study with a primary aim of investigating ERG anomalies in schizophrenia. Thus, the choice of fERG test parameters in this study were derived from Demmin et al., (2018), and the data from schizophrenia patients and healthy controls were previously reported in that paper.

2.2.3. ERG variables and measurements

Outcome measures included amplitude (mV) and implicit time (ms) of the a-wave, b-wave, and PhNR. Amplitude of the a-wave was measured from baseline to the negative trough, and b-wave was measured from the a-wave trough to b-wave peak (Creel 2015). Implicit time was measured from flash onset to the response trough or peak (McCulloch et al. 2015). PhNR data were derived from test P_2 and included the standard metrics of minimum amplitude (measured from the b-wave peak to minimum PhNR trough), amplitude at 72 ms post-stimulus (measured 72 ms after stimulus onset), and implicit time (measured from stimulus onset to minimum PhNR trough). The speed of stimuli presentation in the photopic flicker test (P_F), intended to isolate cone functioning (Young et al. 2012), gave rise to a series of positive peaks only, for which peak-to-peak amplitude and implicit time (i.e., average time between positive peaks) were measured.

2.3. Statistical analyses

Group differences in demographic variables were tested in a series of one-way analyses of variance (ANOVAs; followed by Scheffé post-hoc comparisons) or using pairwise chi-square tests of independence in the case of categorical data. Amplitudes and implicit time fERG measurements were then compared in eight mixed-model ANOVAs. Two 3 × 3 ANOVAs of fERG amplitudes (a-wave and b-wave) were conducted for each adaptation condition (photopic, scotopic), with stimulus condition as the within-subjects factor and diagnostic group (SCZ, MDD, HC) as the between-subject factor. ERG implicit time measurements were analyzed in four additional mixed ANOVAs using the same approach. In the case of significant interactions or main effects of group, one-way ANOVAs followed by Scheffé tests were conducted. One-way ANOVAs were also used to compare flicker test and PhNR amplitude and implicit time, across groups. Correlations between fERG variables and BDI-II total scores were also performed. All statistical analyses were conducted using SPSS (Version 25).

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3. Results

There were no significant differences between samples in terms of age, sex, race, ethnicity, or parental level of education (Table 1). Table 2 presents the group means and standard deviations for each fERG test parameter.

3.1. Amplitude

The ANOVA performed on the three photopic a-wave amplitude measurements revealed a significant group x condition interaction (F (2.46, 88.68) = 3.85, p = .02, η_p^2 = 0.10). Follow-up one-way ANOVAs comparing a-wave amplitude on each of the three photopic tests across groups were significant for conditions P_1 (F (2,72) = 4.20, p = .02) and P_2 (F (2,72) = 4.01, p = .02). Scheffé's post hoc tests revealed the SCZ group (P_1: M = −23.99, SD = 7.21; P_2: M = −3.11, SD = 1.98) demonstrated reduced a-wave amplitudes in comparison to the HC group (P_1: M = −29.50, SD = 6.40; P_2: M = −4.30, SD = 1.59) during the 100 Td-s at 1 Hz, no background condition (P_1; p = .02, d = 0.81) and the 58 Td-s red light and blue background condition (P_2; p = .05; d = 0.66), but neither group differed significantly from the MDD group (P_1: M = −26.51, SD = 6.55; P_2: M = −4.22, SD = 1.33). There were no significant group differences in a-wave amplitude during the 100 Td-s at 2 Hz and 340 Td background (P_3) condition (p > .05; Fig. 1).

A significant group x condition interaction for a-wave amplitude during scotopic conditions (F (3.18, 111.31) = 7.26, p < .001 η_p^2 = 0.17) was again followed by a series of one-way ANOVAs to examine between group differences in a-wave amplitude for each scotopic test condition. There was a significant difference between groups in the 280 Td-s at 0.05 Hz, brightest scotopic condition (S_3; F(2,70) = 6.18, p = .003), where the schizophrenia group (M = −42.19, SD = 11.32) demonstrated an attenuated a-wave amplitude relative to the HC (M = −54.84, SD = 11.72; p = .004, d = 1.10), but not the MDD group (M = −51.24, SD = 15.40). Groups did not significantly differ in a-wave response during less intense scotopic conditions (i.e., S_1 and S_2; p > .05; Fig. 1).

An ANOVA examining b-wave amplitude during photopic test conditions indicated a significant group x condition interaction (F(3.48, 125.38) = 3.95, p = .007, η_p^2 = 0.10). Group differences in b-wave amplitude on each of the three photopic tests were evaluated in one-way ANOVAs, and revealed a significant between-group difference in each condition (P_1: F(2,72) = 5.18, p = .008; P_2: F(2,72) = 3.40, p = .039 P_3: F(2,72) = 5.85, p = .004). Post-hoc Scheffé tests indicated that during the 100 Td-s at 1 Hz, no background condition (P_1), b-wave amplitude in the SCZ group (M = 32.52, SD = 10.24) was reduced compared to HCs (M = 41.37, SD = 11.16; p = .01, d = 0.83). During the 58 Td-s red light and blue background condition (P_2), the b-wave response of the SCZ group (M = 16.22, SD = 6.12) was attenuated in relation to the MDD group (M = 20.59, SD = 6.25, p = .04, d = 0.71). Lastly, in the 100 Td·s at 2 Hz and 340 Td background condition (P_3), the SCZ group (M = 21.13, SD = 8.51) demonstrated a reduction in b-wave amplitude in comparison to both the MDD (M = 28.69, SD = 8.62, p = .008, d = 0.88) and HC (M = 27.36, SD = 7.88, p = .04, d = 0.76) groups (Fig. 2).

There was also a significant group x condition interaction for b-wave amplitude during scotopic conditions (F(3.19, 111.71) = 3.44, p = .02, η_p^2 = 0.09). Follow-up one-way ANOVAs revealed a significant difference between groups in b-wave amplitude during conditions S_2 (F(2, 70) = 8.49, p < .001) and S_3 (F(2,70) = 5.80, p = .005). Post-hoc Scheffé tests indicated that the schizophrenia group (S_2: M = 46.65, SD = 14.40; S_3: M = 58.98, SD = 19.12) demonstrated reduced b-wave amplitudes in comparison to both the MDD (S_2: M = 62.31, SD = 17.21; p = .004, d = 0.99; S_3: M = 76.89, SD = 21.94; p = .01, d = 0.87) and HC groups (S_2: M = 63.33, SD = 15.60; p = .002, d = 1.11; S_3: M = 74.84, SD = 18.78; p = .03, d = 0.84) during the 28 Td-s at 0.1 Hz (S_2) and 280 Td-s at 0.05 Hz conditions (S_3). There were no significant differences between groups in b-wave amplitude during the least intense, 2.8 Td-s at 0.25 Hz, condition (S_1; Fig. 2).

In summary, SCZ patients demonstrated attenuated photopic and scotopic a-wave amplitude in comparison to the HC group (i.e., P_1; P_2; P_3; S_3). In the SCZ group, photopic and scotopic b-wave amplitudes were reduced when compared to both MDD (i.e., P_2; P_3; S_2; S_3) and HC (i.e., P_1; P_3; S_2; S_3) groups.

3.2. Implicit time

The ANOVA examining a-wave implicit time during photopic tests revealed a significant group x condition interaction (F(3.53, 127.06) = 5.24, p = .001, η_p^2 = 0.13). In follow-up one-way ANOVAs comparing a-wave implicit time measurements across groups on the three photopic tests there was a significant difference between groups in P_3 implicit time (F(2,72) = 5.37, p = .009). Scheffé post hoc tests revealed that the MDD group (M = 12.23, SD = 0.78) demonstrated prolonged a-wave implicit time in comparison to the SCZ group (M = 11.42, SD = 1.09) during the 100 Td·s at 2 Hz and 340 Td background condition (p = .007, d = 0.85), but did not differ significantly from the HC group (M = 11.87, SD = 0.68). There were no significant differences

Table 2
fERG Means and Standard Deviations for Each Test Parameter.

	SCZ (N = 25)	MDD (N = 25)	HC (N = 25)
Parameter	M(SD)	M(SD)	M(SD)
P_{1a}			
Amplitude (μV)	−23.99(7.21)	−26.51(6.55)	−29.50(6.40)
Implicit Time (ms)	14.39(1.56)	13.69(0.69)	13.90(1.07)
P_{1b}			
Amplitude (μV)	32.52(10.24)	39.74(9.59)	41.37(11.16)
Implicit Time (ms)	36.19(2.24)	35.70(1.88)	35.01(1.74)
P_{2a}			
Amplitude (μV)	−3.11(1.98)	−4.22(1.33)	−4.30(1.59)
Implicit Time (ms)	11.84(0.67)	12.15(0.76)	12.00(0.96)
P_{2b}			
Amplitude (μV)	16.22(6.12)	20.59(6.25)	18.56(5.40)
Implicit Time (ms)	30.24(1.22)	29.64(1.33)	29.42(1.49)
PhNR			
Min. Amplitude (μV)	−4.91(3.49)	−5.87(2.13)	−7.17(5.36)
Amplitude 72 ms (μV)	−2.96(2.45)	−4.12(1.74)	−4.97(2.95)
Implicit Time (ms)	78.41(8.41)	73.67(5.01)	80.27(10.19)
P_{3a}			
Amplitude (μV)	−6.82(2.43)	−7.77(2.56)	−7.51(3.20)
Implicit Time (ms)	11.42(1.09)	12.23(0.78)	11.87(0.68)
P_{3b}			
Amplitude (μV)	21.13(8.51)	28.69(8.62)	27.36(7.88)
Implicit Time (ms)	32.31(1.67)	31.97(1.70)	31.12(1.61)
P_F			
Amplitude (μV)	19.98(6.60)	27.41(7.44)	26.84(6.92)
Implicit Time (ms)	25.98(1.88)	25.75(1.27)	25.53(1.40)
S_{1a}			
Amplitude (μV)	−10.36(5.44)[a]	−8.30(4.86)[a]	−7.98(3.40)
Implicit Time (ms)	23.00(4.20)[a]	22.14(3.49)[a]	22.43(3.98)
S_{1b}			
Amplitude (μV)	46.06(16.72)[a]	52.97(17.55)[a]	53.44(11.88)
Implicit Time (ms)	62.65(12.16)[a]	61.71(8.57)[a]	61.72(5.78)
S_{2a}			
Amplitude (μV)	−25.10(6.81)[a]	−28.18(11.75)[a]	−28.37(8.55)
Implicit Time (ms)	20.44(20.03)[a]	19.65(1.91)[a]	20.34(2.17)
S_{2b}			
Amplitude (μV)	46.65(14.40)[a]	62.31(17.21)[a]	63.33(15.60)
Implicit Time (ms)	49.09(5.81)[a]	49.63(6.61)[a]	50.78(7.02)
S_{3a}			
Amplitude (μV)	−42.19(11.32)[a]	−51.24(15.40)[a]	−54.84(11.72)
Implicit Time (ms)	12.09(1.15)[a]	12.07(0.79)[a]	12.27(1.06)
S_{3b}			
Amplitude (μV)	58.98(19.12)[a]	76.89(21.94)[a]	74.84(18.78)
Implicit Time (ms)	51.16(6.48)[a]	50.11(5.65)[a]	49.67(4.43)

P = photopic, S = scotopic, PhNR = photopic negative response, $_a$ = a-wave, $_b$ = b-wave, $_F$ = flicker test, μV = microvolts, ms = milliseconds.
[a] N = 24.

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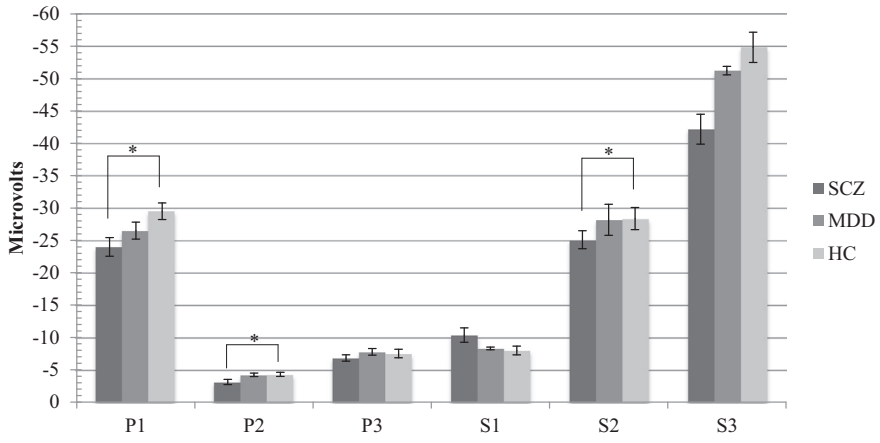

Fig. 1. a-wave amplitude during photopic and scotopic conditions. There was a significant difference between groups in a-wave amplitude for photopic conditions P_1 (F (2,72) = 4.20, p = .02) and P_2 (F (2,72) = 4.01, p = .02), and scotopic condition S_3 (F(2,70) = 6.18, p = .003), with the SCZ group demonstrating attenuated a-wave amplitudes in comparison to the HC group, but neither differing significantly from the MDD group. There were no significant differences between groups in a-wave amplitude for conditions P_3, S_1, or S_2 ($ps > 0.05$). Error bars represent standard errors.

between groups in a-wave implicit time during the 100 Td-s at 1 Hz and no background (P_1) or 58 Td-s red light and blue background condition (P2) conditions. For a-wave implicit time during scotopic conditions, there was no main effect of group and no significant group x condition interaction ($ps > 0.05$).

In the ANOVA examining b-wave implicit time during photopic conditions, there was a significant main effect of group (F(2,72) = 3.65, p = .03, $\eta_p^2 = 0.09$), but no significant group x condition interaction. Post-hoc Scheffé tests revealed a significant difference between groups in b-wave implicit time during the 100 Td-s at 2 Hz and 340 Td background condition (P_3; p = .05, d = 0.73), where the SCZ group (M = 32.31, SD = 1.67) demonstrated increased b-wave implicit time in relation to the HC group (M = 31.12, SD = 1.61). There were no significant differences between groups in b-wave implicit time measurements for any other photopic tests ($ps > 0.05$). Finally, there were no significant main effects of group, nor significant group x condition interactions for b-wave implicit time measurements during scotopic conditions ($ps > 0.05$).

In sum, MDD patients demonstrated longer photopic a-wave implicit time in comparison to SZ patients (i.e., P_3), while prolonged photopic b-wave implicit time was observed in the SCZ group relative to controls (P_3).

3.3. Photopic Negative Response

Groups did not differ significantly in minimum PhNR amplitude ($p >$ .05), however, there was a significant difference between groups in PhNR amplitude measured at 72 ms post-stimulus (F(2,72) = 3.63, p = .03). Scheffé post hoc tests indicated that the SCZ group (M = −2.96, SD = 2.45) demonstrated reduced PhNR amplitudes at 72 ms post-stimulus in comparison to the HC group (M = −4.79, SD = 2.95; p = .03, d = 0.67), but not the MDD group. Implicit time of minimum PhNR amplitude also varied significantly between groups (F(2,72) = 4.35, p = .02): specifically, minimum PhNR amplitude occurred earlier in the MDD group (M = 73.67, SD = 5.01) as compared with the HC group (M = 80.27, SD = 10.19; p = .02, d = 0.82).

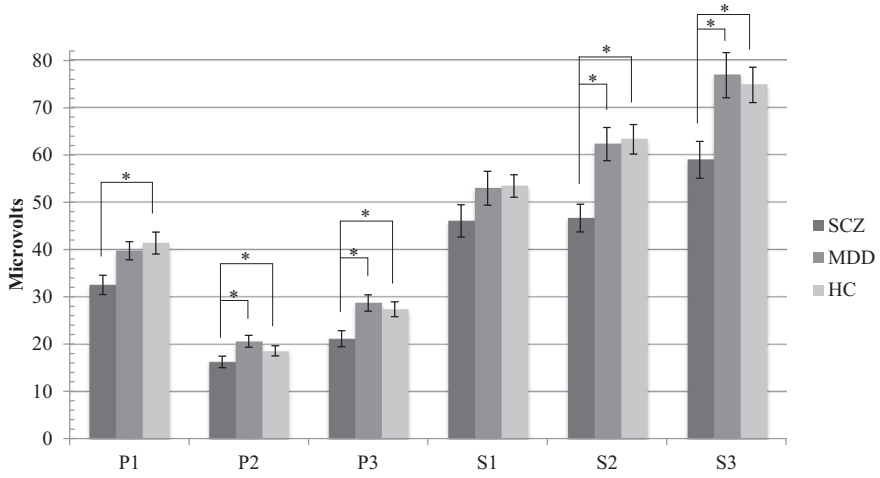

Fig. 2. b-wave amplitude during photopic and scotopic conditions. There was a significant difference between groups in b-wave amplitude during the P_1 condition (F(2,72) = 5.18, p = .008), where the SCZ group demonstrated reduced b-wave amplitude relative to the HC group. There was also a significant difference between groups during P_2 (F(2,72) = 3.40, p = .04) and P_3 (F(2,72) = 5.85, p = .004) photopic conditions and S_2 (F(2, 70) = 8.49, $p < .001$) and S_3 (F(2,70) = 5.80, p = .005) scotopic conditions, where the SCZ group demonstrated reduced b-wave amplitudes in comparison to both the HC and MDD groups. There were no significant differences between groups in b-wave amplitude for condition S_1 ($p > .05$). Error bars represent standard errors.

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3.4. Flicker test

There was a significant difference between groups in flicker test (P_F) amplitude ($F(2,72) = 8.73$, $p < .001$), with Scheffé post hoc tests revealing reduced amplitudes in the SCZ group (M = 19.98, SD = 6.60) in comparison to the MDD (M = 27.41, SD = 7.44; $p = .002$, $d = 1.06$) and HC groups M = 26.84, SD = 6.92; $p = .004$, $d = 1.01$). There were no significant differences between groups in flicker test implicit time measurements.

3.5. Correlations with depressive symptoms

SCZ and MDD groups differed significantly in BDI-II scores, with the MDD group demonstrating higher total scores than the SCZ group ($t(46) = -4.04$, $p < .001$), which was expected given that MDD patients were experiencing a current episode of depression. However, there were no significant correlations between BDI-II scores and fERG amplitude or implicit time variables, even when uncorrected for multiple tests, in either group.

4. Discussion

The goal of this study was to examine whether MDD patients in a current depressive episode would demonstrate anomalies on ERG indices that have differentiated stabilized schizophrenia patients from healthy controls in a previous study. Thus, we measured fERG responses under both photopic and scotopic test conditions, using a variety of stimulus parameters, in order to determine how groups compared to one another.

We observed no differences between the MDD and healthy control groups in the strength of their photoreceptor cell responses. This was the case for a-wave data on both photopic and scotopic tests, as well as for mean amplitude on a steady-state flicker test (assessing cone activity). In contrast, the SCZ group differed from controls on most of these indices, and was significantly different from the MDD group on many of them. There were also no significant differences between the MDD and control groups in b-wave activity during photopic or scotopic tests, suggesting intact functioning of bipolar and Müller cells. Yet, the SCZ group demonstrated many significant differences between both the MDD and control groups in b-wave activity. Finally, the MDD group did not demonstrate the reduction in the PhNR amplitude that was demonstrated in SCZ patients (relative to controls), suggesting intact functioning of retinal ganglion cells in MDD.

While retinal functioning appeared to be largely intact in our acute MDD sample, we did observe an increase in photopic a-wave implicit time in MDD patients relative to stabilized SCZ patients. This finding is consistent with Hébert et al.'s (2017) report of prolonged photopic a-wave implicit time, in an fERG study of the largest MDD sample to date. However, contrary to Hébert et al., we did not observe this difference in comparison to healthy controls. Moreover, in our data the minimum PhNR amplitude occurred earlier in the MDD group as compared with the control group. Despite using similar scotopic test parameters, we also did not observe the same reductions in a- and b-wave amplitudes in MDD that were reported by Hébert et al. (2017).

Findings from a number of prior ERG studies in MDD indicate that anomalies in retinal cell functioning are related to symptom exacerbation and severity (i.e., Bubl et al. 2012; Hébert et al., 2004; Lavoie et al. 2009), with some studies demonstrating a normalization of ERG responses during periods of remission (e.g., summer months in patients who experience a seasonal pattern). These data suggest that ERG anomalies in MDD may be state-related. However, we failed to find this same relationship in our acute MDD sample, even though the majority of the patients in our MDD sample were hospitalized for a depressive episode at the time of their study participation (92%). Further, patients in the MDD group had a mean BDI-II score (M = 26.92, SD = 11.18) within the moderate depression range, with nearly half of participants scoring within the severe range ($n = 12$). Therefore, it is unlikely that our results are inconsistent with prior reports due to milder symptomatology in our MDD group. Another possible explanation for our divergent findings is our choice of test stimuli, which were largely based on prior studies demonstrating ERG anomalies in schizophrenia, and thus may not have been suitable for detecting anomalies in MDD. However, even under those test parameter values that were similar those used in to prior studies of MDD, we did not find evidence of anomalies in retinal cell function in our MDD sample. Alternatively, our somewhat small sample size ($n = 25$) may not have sufficiently powered our analyses, whereas the sizeable medicated MDD group in Hébert et al. (2017; n = 83) may have increased the likelihood of finding an effect. Regarding the latter, however, all of the effect sizes in Hébert et al. were in the small-medium range, and one-tailed statistical tests were used, which, in combination with the large sample size, offered strong sensitivity to even small effects (although this was mitigated somewhat by the use of the false discovery rate procedure to correct for multiple statistical tests). In our study, even using uncorrected p values we did not find evidence of fERG abnormalities in our acute MDD sample. It is possible therefore that while MDD patients do differ from psychiatrically healthy individuals on some aspects of retinal functioning, these anomalies may be subtle, and less pronounced than those observed in stabilized schizophrenia, though these patients were not symptom free and still in need of daily intervention in many cases.

An additional limitation of our study may be the use of the RETeval portable ERG device for data collection. While the RETeval offers several advantages to traditional dome ERG testing (e.g., portability, comfort, ease of administration), the use of DTL or corneal contact electrodes would likely have resulted in less noise and greater signal strength. Nevertheless, using skin electrodes we were able to detect numerous differences in retinal cell signaling in schizophrenia, compared to the other two groups, suggesting the electrodes were able to adequately capture meaningful group differences. It is still possible, however, that had we used a more conventional dome-based recording method for ERG, along with the more sensitive DTL electrodes, both as used in the Hébert et al. (2017) study, we may have detected a greater degree of anomalous performance in the MDD group. This again relates to the issue of the magnitude of the MDD-related alteration though since the portable RETeval device along with skin electrodes is sufficiently sensitive to detect multiple ERG anomalies in schizophrenia and in cases of retinal disease (Al-Otaibi et al. 2017; Grace et al. 2017). Lastly, participants underwent a relatively brief dark adaptation period prior to scotopic test administration (10 min), which may have resulted in a less rod-driven and more cone-driven response during scotopic tests. However, the differences between findings after 10 vs. 20 min of dark adaptation are relatively small, and only minor reductions in amplitude have been observed after 10 min of dark adaptation (Hamilton and Graham 2016). Nevertheless, it is possible that 20 min of dark adaptation (the International Society for Clinical Electrophysiology of Vision [ISCEV] recommended standard; Marmor et al. 2009) might have resulted in greater differences between the acute MDD and the stabilized SCZ, and healthy control groups.

It is also worth noting the possible effects of medication on ERG responses in both patient groups in this study. While in one study in schizophrenia reductions in a-wave amplitude were observed upon hospital admission and were significantly normalized after eight weeks of treatment with antipsychotic medication (Balogh et al. 2008), reductions in b-wave amplitudes have also been reported in samples of non-affected offspring of parents with schizophrenia or bipolar disorder (genetic high-risk sample; Gagné et al. 2019; Hébert et al. 2010), indicating that some fERG abnormalities are observed in medication free samples. Additionally, in the SCZ patient group in this study, there were no significant correlations between chlorpromazine equivalent dosages and fERG amplitudes or implicit times (reported in Demmin et al. 2018). A lack of a relationship between antipsychotic medication dose and ERG findings in schizophrenia and bipolar disorder

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groups was also reported in a recent study (Hébert et al. 2019). Results from Hébert et al. 2017 suggest that among MDD patients, psychotropic medication may normalize reductions in photopic a-wave and b-wave amplitudes at Vmax. However, Fornaro et al. (2011) observed that scotopic b-wave amplitudes were significantly higher in MDD patients who responded after 12 weeks of antidepressant (duloxetine) treatment, and in final responders b-wave amplitude was significantly normalized (i.e., decreased). Therefore, although it is possible that medication had an impact on the ERG responses of MDD patients in this study, the potential direction of this effect is unclear.

5. Conclusion

These data indicate that MDD patients currently experiencing a major depressive episode requiring hospitalization resemble psychiatrically healthy controls on fERG indices that have previously been shown to discriminate stabilized schizophrenia patients from controls. While we cannot rule out the possibility that MDD is associated with retinal functioning anomalies on other fERG indices or test parameters, prior research on this issue suggests that if/when such anomalies exist they are likely to be less severe than those observed in schizophrenia, and possibly much less severe if compared to a schizophrenia group with an equal proportion of hospitalized cases.

Conflict of interest

All authors declare that they have no actual or potential conflicts of interest.

Contributors

Steven Silverstein and Matthew Roché designed the study. Docia Demmin conducted the analyses and wrote the first draft of the manuscript, with input from all authors. Docia Demmin and Roni Netser collected study data. Judy Thompson trained staff on diagnostic and clinical assessments and reviewed interview data from study patients to confirm diagnoses in a weekly diagnostic consensus meeting with study staff. All authors contributed to and approved the final manuscript.

Role of funding source

This study was not funded by an external source.

Acknowledgment

The authors thank the study participants for taking part in this research.

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Please cite this article as: D.L. Demmin, R. Netser, M.W. Roché, et al., People with current major depression resemble healthy controls on flash Electroretinogram indices as..., Schizophrenia Research, https://doi.org/10.1016/j.schres.2019.07.024