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Retinal ganglion cells dysfunctions in schizophrenia patients with or without visual hallucinations

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ABSTRACT

The electroretinogram has revealed photoreceptor, bipolar cell, and, in one prior study, retinal ganglion cell (RGC) dysfunction in schizophrenia. The structural abnormalities of the RGC are well documented in schizophrenia and such abnormalities have been associated with visual hallucinations (VH) in neurological disorders. The goals of this study were: 1) to examine the functional responses of photoreceptors and RGC in schizophrenia patients in comparison with healthy controls; and 2) to compare the extent of retinal dysfunction in schizophrenia patients with or without VH.

We recorded the flash electroretinogram in scotopic and photopic conditions, and the pattern electroretinogram, in schizophrenia patients ($n = 29$) and healthy controls (n = 29). Schizophrenia patients were divided in two groups: schizophrenia patients with VH (VH group, $n = 12$) and schizophrenia patients with auditory hallucinations or no hallucinations (AHNH group, $n = 17$).

Our results replicate previous findings regarding photoreceptor dysfunction in schizophrenia. PERG results showed a significant increase of the P50 implicit time in schizophrenia patients compared with controls ($t(55) = 2.1$, $p < .05$, $d = 0.55$) and a significant increase of the N95 implicit time in schizophrenia patients compared with controls ($t(55) = 4.2$; $p < .001$, $d = 0.66$). We found an increased rod b-wave implicit time (dark-adapted 0.01 ERG) in the VH group compared to the AHNH group and to the control group, which was associated with lifetime VH score.

Our results demonstrate a slowing of RGC signaling in schizophrenia patients, which could affect the quality of visual information reaching the visual cortex. The implications of the data for understanding VH in schizophrenia are discussed.

1. Introduction

Impaired visual processing is well documented in schizophrenia (Butler and Javitt, 2005; Butler et al., 2008; Silverstein and Keane, 2011). It can be observed even in basic visual functions such as visual acuity (Viertiö et al., 2007), contrast sensitivity (Skottun and Skoyles, 2007) and motion processing (Kandil et al., 2013). As the very first step in visual processing, the retina has become a subject of interest in schizophrenia research in the last decade and studies have shown that schizophrenia patients are characterized by multiple structural and functional abnormalities of the retina (Adams and Nasrallah, 2018; Silverstein and Rosen, 2015), which may both parallel abnormalities in the brain and affect visual perception by lowering the quality of information that reaches the brain. For example, it has been proposed that noisy sensory signals may affect the way the patients interpret and adapt to their environment (Silverstein, 2016), and compensatory responses to noisy visual information may lead to a range of cognitive impairments and symptoms in the disorder (Silverstein et al., 2017b). The flash electroretinogram (fERG) is a reliable electrophysiological measurement tool that can be used to study retinal dysfunctions in psychiatric research (Lavoie et al., 2014; Schwitzer et al., 2015). In schizophrenia, early results have mainly shown photoreceptor and bipolar cell dysfunction with reduced cone b-wave amplitude (Gerbaldo et al., 1992), and reduced rod a- and b-wave amplitude in scotopic conditions and reduced cone a-wave amplitude in photopic conditions (Balogh et al., 2008; Warner et al., 1999). Balogh et al. (2008) and Warner et al. (1999) performed correlational analyses and found that ERG abnormalities were not related to antipsychotic medication

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dosages. Similarly, Gerbaldo et al. (1992) reported that ERG abnormalities were not related to antipsychotic medication, as drug-free schizophrenia patients had similar abnormalities to medicated patients.

Moreover, reduced photoreceptor responses have been linked to psychotic symptoms and/or stage of illness (Balogh et al., 2008). More recently, in a study of 105 patients, Hébert et al. (2015) provided strong support for photoreceptor and bipolar cell dysfunction with reduced photopic a- and b-wave amplitudes, scotopic b-wave amplitude, mixed rod cone b-wave amplitude and increased b-wave implicit time in schizophrenia. The b-wave amplitude may be a trait-marker for schizophrenia or severe mental illness, as its reduction has also been observed in unaffected offspring of a parent with schizophrenia or bipolar disorder (Hébert et al., 2010).

Retinal ganglion cells (RGC) are of particular interest since they represent the last stage of retinal processing and the first stage in providing responses in the form of action potentials, along the subcortical visual pathways (Famiglietti and Kolb, 1976). In addition, RGC share properties with cortical neurons, such as anatomical structure, functions and neurotransmitters (dopamine, serotonin, glutamate and γ-aminobituric (Schwitzer et al., 2017b). Hence, RGC functions have been widely studied in various psychiatric disorders such as major depressive disorder (Bubl et al., 2010), autism spectrum disorders (Tebartz van Elst et al., 2015), attention deficit hyperactivity disorder (Bubl et al., 2015) and cannabis use disorder (Schwitzer et al., 2017a; Schwitzer et al., 2018). Surprisingly, RGC functions have been minimally explored in schizophrenia and to our knowledge only one recent study has shown that RGC responses are disrupted in schizophrenia (Demmin et al., 2018). This study measured the photopic negative response (PhNR). PhNR occurs after the b-wave (generated by the bipolar-Muller cell complex) in certain photopic conditions and is considered to be a measure of RGC function (Machida, 2012; Viswanathan et al., 1999). However, this finding needs to be replicated and extended, and ideally an extension would include pattern ERG (pERG) measures, which are the gold standard measures of RGC function according to the International Society for Clinical Electrophysiology of Vision (ISCEV) (Bach et al., 2013). Pattern ERG provides two main measurements: 1) the P50, which is generated by RGC with a contribution of bipolar cells and relates to the spatial distribution and density of the RGC bodies (Holder et al., 2010); and 2) the N95 wave, which represents ganglion cell activity almost exclusively (Froehlich and Kaufman, 1993; Hull and Thompson, 1989) and is considered to be the best marker of RGC (Bach et al., 2013; Holder et al., 2010). Pattern ERG data reporting necessitates averaging a high number of responses, thereby ensuring the reproducibility of the results (Holder et al., 2010). In addition to clarifying aspects of RGC function, the pERG reveals useful information about the integrity of visual information that leaves the retina on the way to the first synapses in the brain.

Multiple functional and structural abnormalities of the retina have also been reported in Parkinson's disease and Lewy body dementia which are neurological disorders in which, like schizophrenia, psychotic symptoms such as visual hallucinations (VH) can occur (Bernardin et al., 2017). Visual hallucinations are a common symptom of schizophrenia and recent studies have shown that lifetime prevalence can reach 37% (Van Ommen et al., 2016). Despite similarities between structural and functional retinal abnormalities in schizophrenia and neurological disorders with VH, the potential association of VH and retinal abnormalities in schizophrenia has not yet been studied.

The main goal of this study, therefore, was to explore the functional responses of photoreceptors and RGC in schizophrenia patients in comparison with healthy controls. A secondary goal was to compare the extent of retinal dysfunctions in schizophrenia patients with or without VH.

2. Materials and methods

2.1. Study population

This study is part of a larger project, Causa Map, which is researching the effect of regular cannabis use on the visual system (Schwitzer et al., 2017a). Twenty-nine schizophrenia patients and 29 healthy matched controls were recruited (Table 1). Before taking part in the study, volunteers provided a detailed psychoactive drug and medical history, underwent a full psychiatric evaluation, and signed consent forms detailing all aspects of the research. All participants received payment in the form of €100 (approximately US $110) in gift vouchers. The study protocol met the requirements of the Declaration of Helsinki (World Medical Association, 2013) and was approved by the Nancy University Hospital Ethics Committee (2013-A00097-38 CPP 13.02.02). The study was registered with clinicaltrials.gov (identifier: NCT02864680).

The modalities of recruitment and inclusion criteria of healthy controls are described in Schwitzer et al. (2017a). The patients with schizophrenia were recruited at the Centre Psychothérapique de Nancy. Patients fulfilled the DSM IV-TR Axis I Disorders criteria forschizophrenia. They were clinically stable on antipsychotic medication, and had no history of neurologic disease. In all enrolled cases, the urine toxicology test showed no evidence of illicit drug or opiate substitution treatment use. It should be noted that cannabis abuse disorder was not an exclusion criterion, in order to facilitate recruitment, although presence/absence of this disorder was considered in the statistical analysis. Among the 29 patients with schizophrenia, 3 were cannabis users and tested positive on THC right before the ERG measurements, and 16 were alcohol users. Among controls, none reported alcohol or THC dependence. Any potential participant reporting drug or alcohol dependence was excluded from the study. For healthy controls, alcohol dependence was assessed following DSM IV criteria using the Mini-International Neuropsychiatric Interview. For schizophrenia patients, alcohol dependence was assessed according to their score in the Alcohol Use Disorders Identification Test (AUDIT), using the AUDIT cutoff score of 15 for men and 13 for women proposed by Rubinsky et al. (2010).

All participants had normal results on ophthalmic evaluation, which included visual acuity and fundoscopic examinations. None of the participants reported visual symptoms, and none was found to have any media opacities.

2.2. Clinical and biological assessments

Control subjects underwent global psychiatric evaluation using the Mini-International Neuropsychiatric Interview (Hergueta et al., 1998) to exclude the presence of a current psychiatric episode. The Positive and Negative Symptoms Scale (PANSS) (Kay et al., 1987) was administered to schizophrenia patients to assess current positive (psychotic) and negative symptoms as well as general psychopathology symptoms (e.g., depression, anxiety) (Table 1). Current (past month) and lifetime visual and auditory hallucinations was specifically evaluated using the

Table 1
Demographic, clinical and substance use characteristics of schizophrenia patients and controls.

	Controls $N = 29$	Schizophrenia patients N = 29	p
Sex: men/women (%)	83/17	79/21	–
Age (years)	24 [23:27]	24 [25:31]	n.s
Education (years)	15 [14:16]	12 [12:13]	$p < .001$
AUDIT	3 [2:4]	1 [1:3]	$p < .05$
Fagerström test score	0	0 [1:3]	n.s
CAST ($N = 3$)	0	0 [0:1]	n.s
PANSS - Global	NA	64 [57:68]	–
PANSS - Positive	NA	13 [12:16]	–
PANSS - Negative	NA	16 [15:19]	–
PANSS - General	NA	31 [28:34]	–
Chlorpromazine equivalent	NA	416 [369:566]	–
Diazepam equivalent (N = 3)	NA	0 [−2:7]	–

Data are presented as median [95% CI].
AUDIT: Alcohol Use Disorder Identification Test score.
CAST: Cannabis Use Screening Test score.
PANSS: Positive and Negative Syndrome Scale.
NA: Non-Applicable.

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Psycho-Sensory hAllucination Scale (PSAS) which provides a repercussion index based on the frequency, duration, negative aspects, conviction, impact, control and sound intensity (for auditory hallucinations) (de Chazeron et al., 2015). The characteristics of the hallucinations and PSAS scores among schizophrenia patients are detailed in Table 3. Regarding 3 schizophrenia patients with significant cannabis use, the PSAS was used to determine whether any hallucinations were induced by THC, and all of these patients clarified that none of their visual hallucinations followed use of THC. Depression was evaluated using the Mongomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979). In addition, the Cannabis Abuse Screening Test, Fagerstrom Test, and AUDIT were performed to assess use, abuse, or dependence with respect to cannabis, tobacco, and alcohol, respectively in both groups of subjects (Table 1).

2.3. ERG measurements

The MonPackOne system (Metrovision) was used for stimulation, recording, and analysis of the fERG and pERG. Electrical signals were recorded simultaneously for both eyes (averaged for analysis) on nondilated pupils for pERG measures and dilated pupils for fERG measures, with Dawson-Trick-Litzkow (DTL) electrodes (Metrovision) placed at the bottom of the conjunctival sac. Ground and reference electrodes were attached to the participant's forehead and external canthi.

RGC functions were explored using pERG measurements recommended in the ISCEV standards (Bach et al., 2013). Photoreceptor responses were explored using fERG measurements that complied with the ISCEV standards (McCulloch et al., 2015). Measurements were conducted in the following sequence: pERG, pupillary dilatation using Tropicamide 0.5% and 20 min dark adaptation, dark-adapted 0.01 ERG (rod response), dark-adapted 3.0 ERG (combine cone-rod response), 10 min light adaptation, light-adapted 3.0 ERG (cone response) and light-adapted 3.0 Flicker ERG (30 Hz Flicker). The conditions of recording, characteristics of measurements and analysis of PERG and flash ERG are described in Schwitzer et al. (2018).

2.4. Statistical analysis

Statistical analyses were conducted using STATISTICA 10 software (StatSoft Inc.). After complete data collection, the data were examined for outliers. Regarding the quality of the electrophysiological signal, outlier trials can occur due to poor patient compliance with keeping eyes wide open during testing, failure to maintain a steady posture, drying of eyes, etc. Hence, we discarded the participants with outlier trials according to the presence of both statistical (below or above 2 standard deviations from the mean) and electrophysiological (quality of the signal) criteria.

For variables characterized by normal distributions, as indicated by non-significant values on the Shapiro-Wilk test, differences between groups were analyzed using an independent samples *t*-test (in cases where two groups were compared) and an analysis of variance (ANOVA) followed by a Tukey test for post-hoc comparisons to determine pairwise differences when more than two groups were compared. For scores with a non-normal distribution, the Mann-Whitney *U* test and the Kruskal-Wallis ANOVA were used. Correlation analyses were conducted with the Spearman rank order correlation test. All results and statistical analysis are displayed in Tables 3 and 4.

3. Results

3.1. Comparisons between schizophrenia patients and controls

3.1.1. Demographic and clinical characteristics

The demographic and substance use characteristics of the participants are described in Table 1. There was no significant difference between the controls (median = 24.0 [IC 95%, 23:27]) and the schizophrenia patients (24.0 [25:31]) ($U = 384.5$, p = n.s) for age. Differences were noted between the groups in terms of years of education (controls: 15.0 [14:16] and schizophrenia patients: 12.0 [12:13]) ($U = 95.5$; $p < .001$). Among the 29 schizophrenia patients, 3 were cannabis users as noted above (and they tested positive for THC), and 16 were alcohol users. No difference was found between controls and schizophrenia patients for CAST scores (controls: 0 and schizophrenia patients: 0 [0:1]) ($U = 364.0$, p = n.s), and AUDIT scores were significantly higher in the control group compared to schizophrenia patients (controls: 3 [2:4] and schizophrenia patients: 1 [1–3]) ($U = 284.5$; $p < .05$) (T1).

3.1.2. pERG parameters (P50 and N95 amplitudes and implicit times)

The MANOVA on the P50 and N95 amplitudes and implicit times revealed a significant effect of group ($F_{4, 54} = 6.9$, $p < .0005$, λ (Wilks) = 0.6, partial $\eta^2 = 0.3$).

For the P50 wave, univariate results revealed no significant effect of group for P50 amplitude ($F_{1, 54} = 0.4$, p = n.s) and a significant increase of the P50 implicit time in schizophrenia patients compared to controls ($F_{1, 54} = 4.3$, $p < .05$).

For the N95 wave, there was not a significant effect of group for N95 amplitude ($F_{1, 54} = 0.2$, p = n.s), but there was a significant increase in the N95 implicit time in schizophrenia patients compared to controls ($F_{1, 54} = 18.0$, $p < .0001$) (Table 2, Fig. 1).

Spearman rank-order correlations showed no significant correlations between P50 and N95 amplitudes and implicit times on the one hand, and CAST score, AUDIT score and number of joints per week on the other, in either the schizophrenia or control group.

3.1.3. Dark-adapted 0.01 fERG parameters (b-wave amplitude and implicit time)

The MANOVA on b-wave amplitudes and implicit times revealed a significant effect of group ($F_{2, 49} = 4.1$, $p < .05$, λ (Wilks) = 0.8, partial $\eta^2 = 0.1$).

Univariate results showed no significant effect of group for b-wave implicit time ($F_{1, 49} = 0.8$, p = n.s) and a significantly reduced b-wave amplitude in patients with schizophrenia compared to controls ($F_{1, 49} = 5.5$, $p < .05$) (Table 2).

Spearman rank-order correlations performed in the schizophrenia patients group for b-wave amplitudes showed a significant correlation with the PANSS general psychopathology score ($r = -0.40$, $p < .05$) indicating that the higher the PANSS general psychopathology score, the lower the amplitudes. No significant correlations were found between b-wave amplitude and implicit time on the one hand, and CAST score, AUDIT score and number of joints per week on the other hand, in either group.

3.1.4. Dark-adapted 3.0 fERG parameters (a and b-wave amplitudes and implicit times)

The MANOVA on the a- and b-wave amplitudes and implicit times revealed a significant effect of group ($F_{4, 45} = 8.4$, $p < .0001$, λ (Wilks) = 0.6, partial $\eta^2 = 0.4$).

For a-wave parameters, univariate results indicated a trend towards reduced a-wave implicit time in schizophrenia patients compared to controls ($F_{4, 45} = 3.4$, $p = .06$), and a significantly reduced amplitude in schizophrenia patients compared to controls ($F_{4, 45} = 22.2$, $p < .0001$). For b-wave parameters, univariate results revealed no significant between-group effect on b-wave implicit time ($F_{4, 45} = 1.9$, p = n.s), and a significantly reduced b-wave amplitude in schizophrenia patients compared to controls ($F_{4, 45} = 7.7$, $p < .01$) (Table 2).

Spearman rank order correlations performed in the schizophrenia group showed a significant correlation between PANSS negative syndrome score and a-wave implicit time ($r = 0.45$, $p < .05$) indicating that a higher level of negative symptoms was related to longer implicit times. No significant correlations were found between a- and b-wave amplitudes and implicit times on the one hand, and CAST score,

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Table 2
Summary of the comparisons between schizophrenia patients and controls.

	Controls	Schizophrenia patients	p, partial η^2
pERG:	$N = 28$	N = 29	$p < .0005$, partial $\eta^2 = 0.3$
P50 implicit time	49.4 (3.4)	51.5 (4.0)	$p < .05$
P50 amplitude	2.4 (0.5)	2.6 (0.9)	n.s
N95 implicit time	88.4 (5.4)	95.7 (7.5)	$p < .001$
N95 amplitude	−3.7 (1.0)	−3.6 (1.5)	n.s
Dark-adapted 0.01 fERG:	N = 29	N = 24	$p < .05$, partial $\eta^2 = 0.1$
b-wave implicit time	81.0 (4.8)	82.5 (7.1)	n.s
b-wave amplitude	137.3 (24.0)	117.5 (38.7)	$p < .05$
Dark-adapted 3.0 fERG:	$N = 25$	N = 25	p < .0001, partial η2 = 0.4
a-wave implicit time	24.1 (0.9)	23.4 (1.7)	$p = .06$
a-wave amplitude	−103.3 (13.6)	−82.0 (18.1)	$p < .0001$, $d = 1.33$
b-wave implicit time	47.0 (2.3)	48.2 (3.7)	n.s
b-wave amplitude	170.5 (28.4)	144.2 (38.9)	$p < .01$, $d = 0.78$
Light-adapted 3.0 fERG:	N = 28	$N = 27$	p < .05, partial η2 = 0.2
a-wave implicit time	18.6 (0.7)	17.7 (1.7)	$p < .05$
a-wave amplitude	−10.6 (2.1)	−8.6 (3.0)	$p < .05$
b-wave implicit time	35.8 (0.9)	35.5 (2.1)	n.s[a]
b-wave amplitude	45.9 (8.4)	43.1 (9.5)	$p = .07$

Data are presented as mean (standard deviation).
pERG: Pattern electroretinogram.
fERG: Flash electroretinogram.
[a] Mann-Whitney *U* test.

AUDIT score and number of joints per week on the other hand, in either the patient or control group.

3.1.5. Light-adapted 3.0 fERG parameters (a and b-wave amplitudes and implicit times)

The MANOVA conducted on a-wave amplitude and implicit time and b-wave amplitude revealed a significant effect of group ($F_{3, 52} = 3.7$, $p < .05$, λ (Wilks) = 0.8, partial $\eta^2 = 0.2$). For a-wave parameters, univariate results indicated a significantly reduced a-wave implicit time ($F_{1, 52} = 5.1$, $p < .05$) and a significantly reduced a-wave amplitude in patients with schizophrenia compared to controls ($F_{1, 52} = 4.3$, $p < .05$). For b-wave amplitude, univariate results showed a trend towards reduced b-wave amplitude in schizophrenia patients compared to controls ($F_{1, 52} = 3.3$, $p = .07$) (Table 2).

The Mann-Whitney *U* test showed no significant difference between groups for b-wave implicit time (U = 329.0, p = n.s). No significant correlations were found between a and b-wave amplitudes and implicit times on the one hand, and CAST and AUDIT scores on the other hand, in either patients or controls.

3.2. Comparisons between schizophrenia patients with VH (VH), schizophrenia patients with auditory hallucinations or no hallucinations (AHNH) and controls (C)

The cohort of schizophrenia patients was divided into two groups according to the presence of lifetime VH in their symptomatology: VH group ($N = 12$) and AHNH group ($N = 17$).

3.2.1. Demographic and clinical characteristics

There were no differences between VH and AHNH groups for CAST score, AUDIT score, PANSS scores and antipsychotic medication. No significant differences were found between VH and AHNH groups for

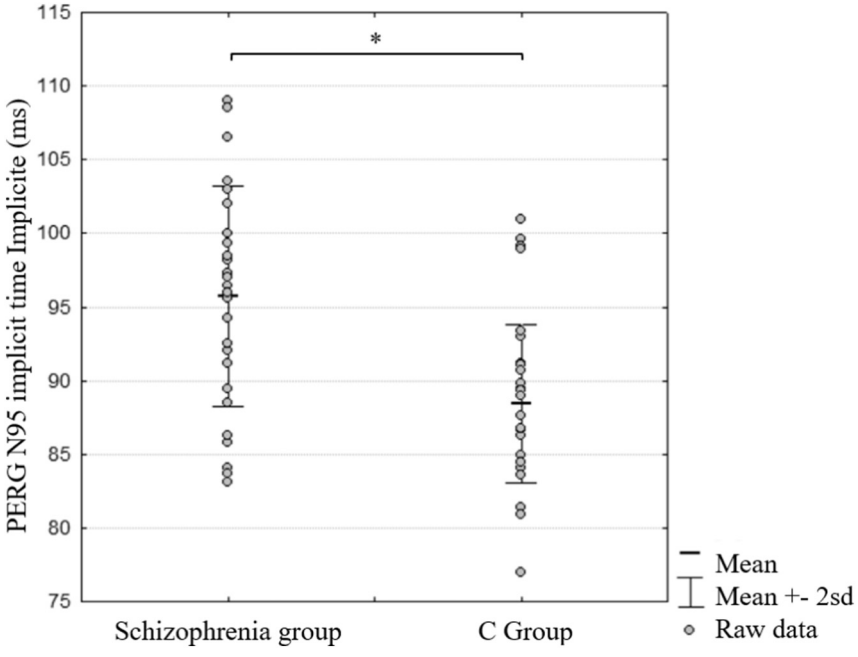

Fig. 1. Pattern ERG N95 Implicit Time (ms) for schizophrenia patients and controls. N95 implicit time is significantly higher in schizophrenia patients (t(55) = 4.2; $p < .001$, $d = 0.66$).

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diazepam equivalent and disease duration (Table 3). The median and 95 confidence interval (95%) of the lifetime AH repercussion index of the PSAS was 0.0 [2.9:11.4] in the AHNH group versus 19.5 [9.2:20.7] in the VH group. The lifetime AH repercussion index of the PSAS was significantly higher in the VH group compared to the AHNH group ($U = 50.0$, $p < .05$, $\eta^2 = 0.18$). The Kruskal-Wallis ANOVA on age and years of education between the VH group, the AHNH group and the controls showed a significant difference between the controls and the VH group ($p < .001$) and the controls and the AHNH group ($H(2, n = 58) = 26.5$, $p < .001$, $\eta^2 = 0.4$) based on years of education (Table 3).

3.2.2. PERG parameters (P50 and N95 amplitudes and implicit times)

The MANOVA on the P50 and N95 amplitudes and implicit times revealed a significant effect of group ($F_{8,54} = 3.8$, $p < .0001$, λ Wilks =0.6, partial $\eta^2 = 0.2$).

For P50 parameters, univariate results revealed a trend towards increased P50 implicit time in the VH group compared to controls ($F_{2,54} = 2.6$, $p = .08$), but no significant differences for amplitude (F2,54 = 0.2, p = n.s).

For N95 parameters, univariate results revealed a significant effect of group for N95 implicit time ($F_{2,54} = 10.5$, $p < .0001$). Post-hoc Tukey test revealed a trend towards an increased N95 implicit time in the VH group compared to controls ($p = .06$), and N95 implicit time was significantly increased in the AHNH group compared to controls ($p < .001$) (Table 4, Fig. 2).

There were no significant correlations between P50 and N95 amplitudes and implicit times on the one hand, and CAST score, AUDIT score and number of joints per week on the other hand, in the VH or AHNH groups or controls.

3.2.3. Dark-adapted 0.01 ERG parameters (b-wave amplitude and implicit time)

The MANOVA on b-wave amplitude and implicit time revealed a significant effect of group ($F_{4, 49} = 4.1$, $p < .005$, λ (Wilks) = 0.7, partial $\eta^2 = 0.1$, $F_{2,49} = 4.1$, $p < .005$, partial $\eta^2 = 0.20$).

For b-wave implicit time, univariate results revealed a significant effect of group ($F_{4, 49} = 4.3$, $p < .05$). Post-hoc Tukey tests indicated a significant increase in b-wave implicit time in the VH group compared to controls ($p < .05$) and the AHNH group ($p < .05$).

For b-wave amplitude, univariate results revealed a significant effect of group ($F_{4, 49} = 3.8$, $p < .05$). Post-hoc Tukey tests indicated a significant decrease in b-wave amplitude in the AHNH group compared to controls ($p < .05$) (Table 4, Fig. 3).

Spearman rank-order correlations performed in the VH group showed a significant correlation between lifetime VH repercussion score and b-wave implicit time ($r = 0.70$, $p < .05$) indicating that the higher the VH repercussion score the longer the implicit time of the b-wave. No significant correlations were found between b-wave amplitude and implicit time on the one hand, and CAST score, AUDIT score and number of joints per week on the other hand, in the VH, AHNH or control groups.

3.2.4. Dark-adapted 3.0 ERG parameters (a and b-wave amplitudes and implicit times)

The MANOVA on a- and b-wave amplitudes revealed a significant effect of group ($F_{4, 47} = 4.8$, p < .005, λ (Wilks) = 0.7, partial η2 = 0.2).

For a-wave parameters, univariate results indicated a significant effect of group for amplitude ($F_{2, 47} = 10.9$, $p < .005$). Post-hoc Tukey tests indicated a significantly reduced a-wave amplitude in the VH group compared to controls ($p < .005$) and in the AHNH group compared to controls ($p < .001$).

For b-wave parameters, univariate results revealed a significant effect of group for b-wave amplitude ($F_{2, 47} = 3.8$, $p < .05$). Post-hoc Tukey tests indicated a trend towards decreased b-wave amplitude in the VH group compared to controls ($p = .06$) and a trend towards decreased b-wave amplitude in the AHNH group compared to controls ($p = .08$) (Table 4).

Kruskal-Wallis ANOVAs conducted for a- and b-wave implicit time did not reveal any significant differences.

Spearman rank-order correlations showed no significant correlations between a- and b-wave amplitudes and implicit times on the

Table 3
Demographic, clinical, substance use characteristics and characteristics of the hallucinations and PSAS scores for the VH and AHNH groups.

	Controls	VH group $N = 12$	AHNH group $N = 17$	p
Sex: men/women (%)	83/17	92/8	71/29	–
Age (years)	24 [23:27]	30 [24:37]	23 [23:30]	n.s
Education (years)	15 [14:16]	12.0 [11:13]	12 [12:13]	$p < .001$ (VH/C and AHNH/C)
AUDIT	3 [2:4]	0.0 [0.0:4.0]	1.0 [0.0:10.0]	n.s
CAST	0	0.0 [0.0:5.0]	0.0 [0.0:5.0]	n.s
Disease duration (months)	NA	87.0 [48.7:188.8]	27.0 [21.2:102.9]	n.s
PSAS LIFETIME:	NA			
Nb. of subjects with VH		12	0	–
Nb. of subjects with AH		10	17	–
Lifetime repercussion score of VH		13.0 [10.2:17.5]	NA	–
Lifetime repercussion score of AH		19.5 [9.2:20.7]	0.0 [2.9:11.4]	$p < .05$
PSAS CURRENT:	NA			
Nb. of subjects with VH		2	0	–
Nb. of subjects with AH		3	1	–
Current repercussion score of VH		0.0 [−0.8:4.3]	NA	–
Current repercussion score of AH		0.0 [−0.6:6.8]	0.0 [−0.9:2.6]	n.s
Chlorpromazine equivalent (mean (sd))	NA	437.8 (230.8)	489 (280)	n.s
Diazepam equivalent	NA	0.0 [−0.7:3.8]	0.0 [−3.8:11.7]	n.s

Data are presented as median [95% CI] and mean (standard deviation) when indicated.
VH group: Schizophrenia patients with Visual Hallucinations.
AHNH group: Schizophrenia patients with Auditory Hallucinations or No Hallucinations.
AUDIT: Alcohol Use Disorder Identification Test score.
CAST: Cannabis Use Screening Test score.
PSAS: PsychoSensory hAllucination Scale.
NA: Non-Applicable.

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Table 4
Summary of the comparisons between the control, VH, and AHNH groups.

	Controls	VH group	AHNH group	p, partial η^2
PERG:	N = 28	N = 12	N = 17	$p < .0001$, partial $\eta 2 = 0.2$
P50 implicit time	49.4 (3.4)	52.2 (4.2)	51.0 (4.0)	$p = .08$
P50 amplitude	2.5 (0.1)	2.6 (0.8)	2.5 (1.0)	n.s
N95 implicit time	88.4 (5.4)	93.5 (7.5)	97.3 (7.2)	$p = .06$ (VH/C) $p < .001$ (AHNH/C)
N95 amplitude	−3.9 (0.2)	−3.5 (1.1)	−3.6 (1.7)	n.s
Dark-adapted 0.01 ERG:	N = 29	*N* = 9	*N* = 15	$p < .005$, partial $\eta^2 = 0.1$
b-wave implicit time	81.0 (4.8)	86.6 (5.5)	80.0 (6.9)	$p < .05$ (VH/C) $p < .05$ (AHNH/C)
b-wave amplitude	137.3 (24.0)	129.3 (30.0)	110.4 (42.4)	$p < .05$ (AHNH/C)
Dark-adapted 3.0 ERG:	N = 25	*N* = 10	N = 15	$p < .005$, partial $\eta^2 = 0.2$
a-wave implicit time	24.1 (0.9)	23.7 (1.9)	23.2 (1.6)	n.s[a]
a-wave amplitude	−103.3 (13.6)	−80.9 (18.8)	−82.6 (18.2)	$p < .005$ (HV/C) $p < .001$(AHNH/C)
b-wave implicit time	47.0 (2.3)	49.1 (4.1)	47.7 (3.4)	n.s[a]
b-wave amplitude	170.5 (28.4)	140.8 (31.2)	146.5 (42.6)	$p = .06$ (HV/C) $p = .08$ (AHNH/C)
Light-adapted 3.0 ERG:	N = 28	*N* = 11	N = 15	$p = .05$, partial $\eta^2 = 0.1$
a-wave implicit time (median [95% CI])	18.6 [18.3–18.9]	18.6 [16.9:19.3]	17.7 [16.4:18.3]	$p = .09$[a]
a-wave amplitude	−10.6 (2.1)	−9.4 (2.5)	−8.0 (3.2)	–
b-wave implicit time	35.8 (0.9)	36.1 (2.2)	35.1 (2.0)	–
b-wave amplitude	45.9 (8.4)	44.3 (10.5)	42.3 (9.1)	–

Data are presented as mean (standard deviation) and median [95% CI] when indicated.
PERG: Pattern Electroretinogram.
ERG: Electroretinogram.
[a] Kruskall-Wallis ANOVA.

one hand, and CAST score, AUDIT score and number of joints per week on the other hand, in any of the groups.

3.2.5. Light-adapted 3.0 ERG parameters (a and b-wave amplitudes and implicit times)

The MANOVA on a- and b-wave amplitudes and implicit times revealed a trend towards a significant effect of group ($F_{4, 52} = 2.4$, $p = .05$, λ (Wilks) = 0.8, partial $\eta 2 = 0.1$).

Kruskal-Wallis ANOVAs conducted for a-wave implicit time and b-wave implicit time revealed a trend towards a between-group effect for a-wave implicit time ($H(2, N = 54) = 4.8$, $p = .09$) (Table 4).

Spearman rank-order correlations showed no significant correlations between a- and b-wave amplitudes and implicit times on the one hand, and CAST score, AUDIT score and number of joints per week on the other hand, in any of the groups.

4. Discussion

4.1. Retinal dysfunctions in schizophrenia patients

The main finding from this study is that schizophrenia patients are characterized by a delay in the output of action potentials by the RGC as shown by an increased in PERG N95 implicit time. We also observed photoreceptor dysfunction in the form of reduced rod a-wave amplitude (dark-adapted 3.0 ERG), and cone a-wave amplitude (light-adapted 3.0 ERG), as well as bipolar cell dysfunction characterized by reduced rod b-wave amplitudes (dark-adapted 0.01 ERG and dark-

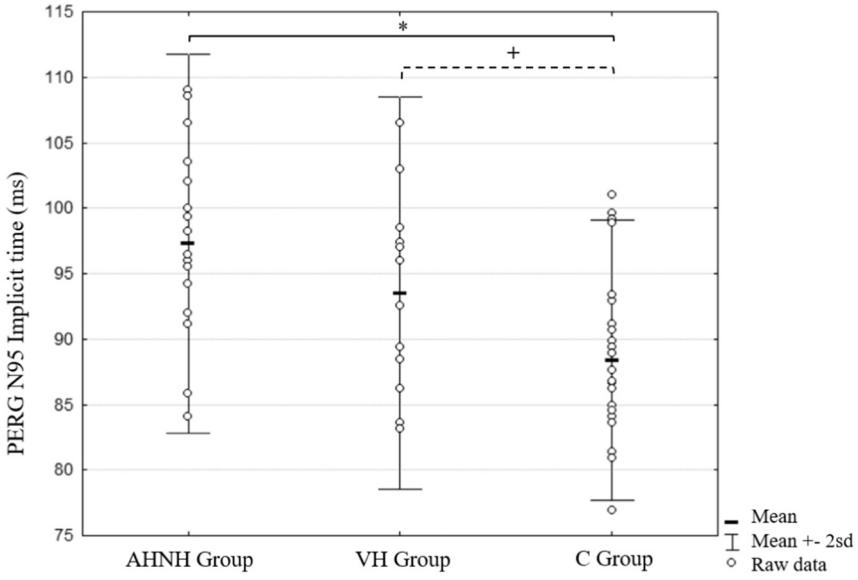

Fig. 2. Pattern ERG N95 Implicit Time in the VH group, the AHNH group and the control group. A trend towards increased N95 implicit time was found in the VH group compared to the control group ($p = .06$) and a significant increase of the N95 implicit time was found in the AHNH group compared to the control group ($p < .001$).

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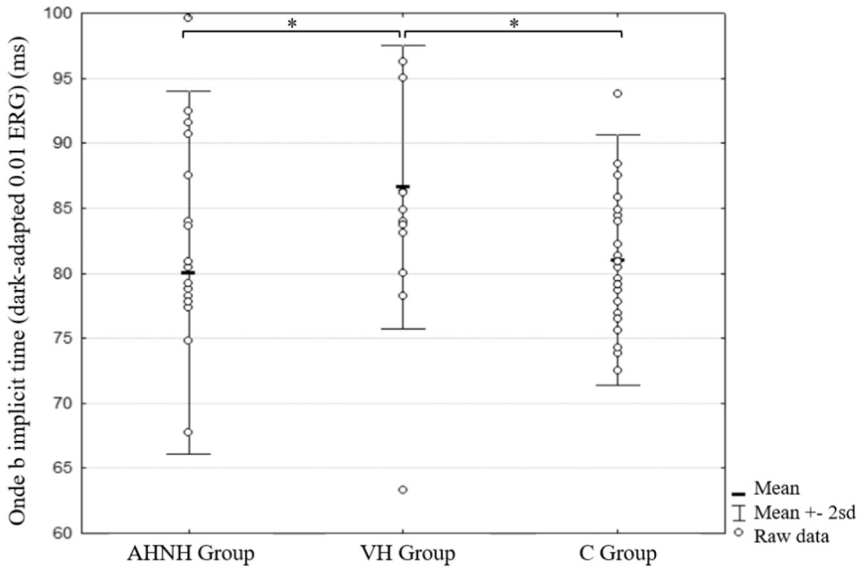

Fig. 3. Dot Plot of flash ERG b-wave implicit time (dark-adapted 0.01 ERG) for the VH group, the AHNH group and the control group. A significant increase of the b-wave implicit time was found in the VH group compared to both the control ($p < .05$) and AHNH groups ($p < .05$).

adapted 3.0), all of which are consistent with previous findings (Balogh et al., 2008; Hébert et al., 2015; Warner et al., 1999).

RGC dysfunctions have been previously found in schizophrenia patients, using the PhNR component of the fERG (Demmin et al., 2018). As a complement to these findings, our study is the first to demonstrate RGC dysfunction in schizophrenia using a pERG protocol that follows ISCEV standards for RGC measurements. The pERG protocol directly targets RGC functions because the photoreceptors are cancelled out upon recording (Porciatti, 2015). Moreover, animal models show that pERG is the most sensitive and acute measure as it produces an immediate effect of RGC dysfunction on PERG recordings (Chou et al., 2013; Yang et al., 2013). In this context, our findings provide strong evidence for a delay of approximatively 7 ms in the transmission of action potentials generated by RGC. These findings thus raise the question of the contribution of RGC dysfunctions to altered V1 activity in schizophrenia. Indeed, visual evoked potentials (VEP) studies have shown reduced P1 amplitude at V1 in schizophrenia patients (Butler et al., 2007; González-Hernández et al., 2014; González-Hernández et al., 2015; Yeap et al., 2006). The relationships between reduced retinal input and V1 activity have been explored using simultaneous recordings of pERG and pattern visual evoked potentials (pVEP) in ophthalmologic disorders (Heravian et al., 2011; Holder, 1997) and neurological disorders (Calzetti et al., 1990; El-Shazly et al., 2017; Krasodomska et al., 2010) providing evidence of a direct link between RGC dysfunctions and V1 dysfunctions in the visual pathway. While, to our knowledge these links remain to be explored in people with schizophrenia, they are supported by a recent computational model of early visual dysfunction in the disorder (Silverstein et al., 2017a).

Glutamate is the main neurotransmitter involved in the vertical transmission of retinal information (Wu and Maple, 1998). Glutamatergic dysfunction is also emphasized in pathophysiological models of schizophrenia (Bossong et al., 2019; Kantrowitz and Javitt, 2012). The hypothesis of a link between reduced RGC responses and glutamatergic dysfunction has been proposed in cannabis consumers due to the effects of tetrahydrocannabinol on retinal endocannabinoids and glutamate transmission (Schwitzer et al., 2017a). Thus, our results could also bring support to the hypothesis of a link between RGC responses and glutamatergic dysfunctions in the specific context of the glutamatergic model of schizophrenia. However, other neurotransmitters, such as dopamine, histamine, GABA, and serotonin, are also active in the retina. Further research is needed to clarify the roles of different neurotransmitters in the retina, and the extent to which these roles are altered in schizophrenia.

One way to explore this question is to examine correlations between psychotic symptoms and retinal dysfunctions. We found a significant correlation between the PANSS general psychopathology factor score and a reduced rod b-wave amplitude (dark-adapted 0.01 ERG), and between the PANSS negative factor score and increased rod a-wave implicit time (dark adapted 3.0 ERG) in schizophrenia patients. Balogh et al. (2008) observed a negative correlation between PANSS positive symptoms and reduced cone response in an acutely psychotic patient sample, and Demmin et al. (2018) observed a relationship between reduced cone responses and negative symptoms in a chronically ill and clinically stable sample. These findings suggest that there are illness state and stage effects on retinal function. In our sample, all patients but one were outpatients for at least several weeks and were following cognitive and psychosocial rehabilitation programs, suggesting that our findings may be more trait- than state-related. On the other hand, five of the twelve patients in the VH group had experienced VH or AH during the past month according to the PSAS, and so the influence of acute or sub-acute psychosis cannot be ruled out. Longitudinal studies comparing retinal responses from the emergence of psychotic symptoms, through antipsychotic medication introduction and the stable phase of treatment can clarify the relationships between illness signs and symptoms and retinal responses, and hence the possible roles of specific neurotransmitters.

4.2. Retinal dysfunctions in schizophrenia patients with VH

The second aim of our study was to explore whether retinal functions are disrupted to a greater degree in schizophrenia patients with a lifetime history of VH. Forty-one percent of our schizophrenia sample experienced VH selectively during the acute phase of psychotic symptoms or as chronic experiences, and two of them had experienced recent VH episodes in the previous month. Ten of the 12 VH patients experienced AH as well and strikingly, the lifetime total score for AH in the VH group was significantly higher compared to lifetime total score for AH in the AH group, which can be related to more severe psychopathology and poorer prognosis in schizophrenia patients with VH (McCabe et al., 1972; Mueser et al., 1990).

To our knowledge no study has explored a possible link between retinal dysfunctions and VH in ophthalmologic, neurological or psychiatric

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disorders, despite indirect arguments regarding structural retinal abnormalities related to VH (Lee et al., 2014; Lee et al., 2016). We found a significant increase of the b-wave implicit time (dark adapted 0.01 ERG) in the VH group compared to the AHNH group and to the control group. Moreover, the b-wave implicit time was significantly correlated with the lifetime VH total score in the VH group, indicating that rod dysfunction was associated with the severity of the VH. This result could indicate an impairment in the functional properties of the rods selectively in patients presenting VH. To our knowledge, rod b-wave implicit time anomalies have never been found specifically in a subgroup of schizophrenia patients with VH. Sensory-impoverished environments, like dark places for example, favor the emergence of VH as sensorial inputs are degraded and interpretation of the visual scene relies more on top-down factors (Collerton et al., 2005; Diederich et al., 2005). Hence, rod dysfunction could contribute to the degradation of bottom-up visual processing as an aggravating factor for developing VH in schizophrenia patients prone to this specific symptom.

Studying retinal dysfunctions as well as structural abnormalities of the retina in VH patients presents several methodological challenges (Kopal et al., 2015). One issue is that characteristics of VH in schizophrenia are somewhat different from VH in neurological disorders. Indeed, in schizophrenia and particularly in our sample, VH is rarely the only modality of hallucination, and this reduces the likelihood of constituting a pure VH group. This is in contrast to disorders such as Parkinson's disease or Lewy body dementia, where VH are by far the most common, and often the only type of, hallucination reported. In addition, VH in schizophrenia are not as recurrent as in these neurological disorders. For example, in our sample, for 10 of our 12 VH patients, VH were experienced mostly during the acute phase and were never experienced during phases of clinical stability. This time course of VH symptoms in schizophrenia points to the need to study retinal dysfunctions as they relate to the acute phase of psychosis, or during the prodromal period, where they may predict risk for psychosis (Klosterkötter et al., 2001).

A limitation of this study was that the potential impact of tobacco use was not considered, despite its effect on synaptic transmission within the central nervous system. The effect of chronic nicotine administration on ERG has not yet been evaluated. Dark-adapted and light-adapted flash ERG responses have been modified after acute nicotine administration in the form of gum 30 min before testing (Varghese et al., 2011), but the effect of regular tobacco use on flash ERG measurements still needs to be evaluated. Future studies should include a control group including tobacco smokers. In the schizophrenia patients group, 3 patients were regular cannabis consumers (2 in the AHNH group and 1 in the VH group). CAST scores were not significantly different between groups but cannabis consumption is associated with retinal dysfunction (Schwitzer et al., 2017a; Schwitzer et al., 2018). Future studies should therefore compare schizophrenia patients with and without a history of cannabis use and quantify the relationships between recent and lifetime cannabis use and ERG findings to the extent possible.

5. Conclusions

In summary, our study replicates previous results for photoreceptor and bipolar cell dysfunctions and lends strong support to RGC dysfunctions in schizophrenia. Our results also demonstrate, for the first time, a relationship between rod dysfunction and VH in schizophrenia. ERG studies are relatively inexpensive to conduct. They provide valid, reliable, and reproducible measurements that can be obtained in clinical settings and that can be used to provide a “window to the brain” (London et al., 2013) in the treatment of people with central nervous system disorders (Schwitzer et al., 2015). Studies of the retina and particularly RGC functions in schizophrenia will contribute to a better understanding of basic visual functions, their role in disturbed higher visual and cognitive functions, and the extent to which they can predict later development of the disorder.

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