Journal of Affective Disorders 295 (2021) 453–462

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research paper

Complete evaluation of retinal function in Major Depressive Disorder: From central slowdown to hyperactive periphery

Eve Cosker [a,b,*], Marie Moulard [a], Cédric Baumann [c], Amandine Luc [c], Karine Angioi-Duprez [d,e], Vincent Laprévote [a,b,e], Raymund Schwan [a,e,f,g], Thomas Schwitzer [a,e,f,g]

[a] Pole Hospitalo-Universitaire de Psychiatrie d'Adulte et d'Addictologie du Grand Nancy, Centre Psychothérapique de Nancy, Laxou, France
[b] INSERM U1114, Fédération de Médecine Translationnelle de Strasbourg, Département de Psychiatrie, Centre Hospitalier Régional Universitaire de Strasbourg, Strasbourg, France
[c] MPI department, Unit of methodology, data management and statistics, University Hospital of Nancy, Vandœuvre-Lès-Nancy, France
[d] Service d'Ophtalmologie, CHRU Nancy, Nancy, France
[e] Faculté de Médecine, Université de Lorraine, Vandoeuvre-lès-Nancy, France
[f] INSERM U1254, Imagerie Adaptive Diagnostique et Interventionnelle (IADI), Vandœuvre-lès-Nancy, France
[g] Fondation Fondamental, Créteil, France

ARTICLE INFO

Keywords:
Major depressive disorder
Major depressive episode
Retina
Electroretinogram
Electrophysiological marker
Retinal function

ABSTRACT

Background: Developing easy-to-access biomarkers is crucial in Major Depressive Disorder. The retina has already been suggested as relevant. However, there is a need for a global and local assessment of whole retinal function using a reproducible, standardized protocol allowing for comparison across studies. Our aim is to assess whole retinal function in patients with actual unipolar Major Depressive Episode (MDE) using pattern, flash and multifocal electroretinogram (ERG) according to the International Society for Clinical Electrophysiology of Vision standardized protocols.

Methods: We assessed retinal function in 14 males and females with MDE, diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders, and in age- and sex-matched healthy controls.

Results: Comparing the patients with the controls, we observed the following using multifocal ERG: a significant increase in N1 peak time in ring 3 and a decrease in P1 amplitude in ring 2; using pattern ERG: a significant increase in P50 peak time; using flash ERG: a decrease in a- and b-wave peak time and an increase in the b-wave amplitude in dark-adapted 3.0, a decrease in a- and b-wave peak time and an increase in both wave amplitudes in light-adapted 3.0, and a decrease in the b-wave peak time in light-adapted flicker.

Limitations: Sample size. Contribution of pharmacological treatments to the outcomes cannot be formally excluded.

Conclusions: Patients with MDE exhibit delayed signaling in the central retina and hyperreactivity to light in the periphery. Central retinal function may be a marker of psychomotor retardation and cognitive impairment in MDE.

1. Introduction

The retina is a part of the central nervous system, formed as a paired evagination from the anterior central nervous system during embryonic development (Hoon et al., 2014; O'Rahilly and Müller, 1994). The human retina consists of three main layers of neurons interconnected by synapses (Hoon et al., 2014) (Fig. 1). The photoreceptors — cones and rods — in the outer nuclear layer and the bipolar cells in the inner nuclear layer emit electrical signals in the form of membrane potential (Hoon et al., 2014). The bipolar cells connect with the ganglion cells. These emit action potential (Baylor, 1996) and their axons form the optic nerve, which transmits visual information to the brain, especially the primary visual cortex, via the optic chiasma and the lateral geniculate nucleus. The position of the retina outside the cranium makes it an accessible part of the central nervous system. Its function is assessed using electroretinogram (ERG), an electrophysiological method that is relatively easy to perform, non-invasive, reproducible and cheap (Holder et al., 2010). An ERG trace reflects the summation of cellular

* Corresponding author: Eve Cosker, centre Psychothérapique de Nancy, 1, rue du Docteur Archambault, Laxou, F-54 520, France.
E-mail address: eve.cosker@cpn-laxou.com (E. Cosker).

https://doi.org/10.1016/j.jad.2021.08.054
Received 18 May 2021; Received in revised form 30 July 2021; Accepted 21 August 2021
Available online 27 August 2021

signals of different origins, occurring at different times to form an overall signal. Use of different ERG techniques makes it possible to evaluate each layer of the neuroretina (Robson et al., 2018). As it is difficult to study the living brain due to its position in the cranium, there is growing interest in retinal assessment in psychiatric disease (Bernardin et al., 2020; Lavoie et al., 2014a, 2014b; London et al., 2013; Schwitzer et al., 2019; Silverstein and Rosen, 2015). In fact, the brain and the retina are both exposed to the same insults and brain anomalies have manifestations in the retina (London et al., 2013). Moreover, they share common neurotransmitters, such as dopamine (Witkovsky, 2004), serotonin (Gastinger et al., 2006), melatonin (Wiechmann and Sherry, 2013), glutamate and gamma aminobutyric acid (GABA) (de Souza et al., 2013; Wu and Maple, 1998). These neurotransmitters have been shown to be involved in the physiology of Major Depressive Disorder (MDD) (Duman et al., 2019; Hamon and Blier, 2013; Niciu et al., 2014).

Case control studies have already assessed retinal function in MDD (Cosker et al., 2020; Schwitzer et al., 2015). Assessing ganglion cells, Bubl et al. found reduced contrast gain in medicated and unmedicated patients with MDD in acute phase compared with healthy controls, with a correlation between disease severity and contrast gain (Bubl et al., 2010). More recently, Demmin et al. also found impairment of the ganglion cells in patients with MDD (Demmin et al., 2020). In contrast, Fam et al. found no significant difference in ganglion cell function between patients with moderate to severe MDD and healthy controls, and no correlation with disease severity (Fam et al., 2013). Assessing photoreceptors and bipolar cells in patients with MDD, in the photoreceptors, Hébert et al. showed a reduced a-wave amplitude in the mixed rod/cone response (Hébert et al., 2017). In the bipolar cells, they found a prolonged b-wave peak time in the cone-bipolar cell response, a reduced b-wave amplitude in the rod-bipolar cell response and an increased b-wave peak time in the mixed rod/cone response (Hébert et al., 2017). Other studies had negative findings (Demmin et al., 2020; Fam et al., 2013; Fornaro et al., 2011). Interestingly, Fornaro et al. found differences at baseline in the rod system in the group of patients with MDD achieving final response (Fornaro et al., 2011). However, to date, no study has assessed the local and global functional properties of the whole retina using mfERG. Moreover, the heterogeneity of the protocols used across studies to assess retinal function contributes to the inconsistent results.

There is therefore a need for homogenous retinal function assessment across studies and to replicate previous results with standardized protocols. The International Society for Clinical Electrophysiology of Vision (ISECV) has established worldwide standardized clinical protocols for retinal electrophysiological examination (Bubl et al., 2010; Hoffmann et al., 2021; McCulloch et al., 2015; Robson et al., 2018). They are detailed, precise, standardized and reproducible and assess the global activity of all layers of the retina as well as topographic measurements of retinal activity. A broad approach with a standardized protocol will allow the confirmation and identification of retinal dysfunctions in MDD. The objective of this study was to evaluate the function of the different retinal stages in patients with MDD in acute phase compared with healthy controls, using standardized, reproducible, electroretinographic measures from the ISCEV protocols: multifocal ERG (mfERG), pattern ERG (PERG), and flash ERG (fERG).

2. Methods

2.1. Population and ethics statement

2.1.1. Participants with mdd

This was an ancillary study conducted with data collected during the single-center, prospective double-blinded randomized LUMIDEP study (NCT03685942) at the Nancy Psychotherapeutic Center (NPC), France to assess the efficacy of light therapy in non-seasonal MDD in acute phase (Cosker et al., 2021). Participants with MDD were recruited from in- and outpatients of the NPC and from outpatients of physicians in private practice. Participants included in the present study were recruited from January 2019 to July 2020. Prior to inclusion, all participants were asked for details of their medical history and treatments and underwent a psychiatric interview. All participants signed consent. Participants agreeing to take part in the ancillary study signed consent forms specific to that study. All participants received compensation in the form of €15 in gift vouchers. The study protocol met the requirements of the Helsinki Declaration and was approved by the Ile-de France X Ethics Committee (no. 34–2018).

2.1.2. Matched healthy controls

Matched healthy controls for sex and age (+/- 5 years) were recruited from those of two other studies, the CAUSAMAP study (NCT02864680) and the ERICA study (NCT0381897).

The single-center, open-label prospective CAUSAMAP study was conducted at Nancy University Hospital, France to investigate visual system function in cannabis users compared with healthy controls. The protocol has been described previously, met the requirements of the Helsinki Declaration and was approved by the Ethics Committee of Nancy University Hospital. (Bernardin et al., 2020; Lucas et al., 2019; Schwitzer et al., 2020, 2018, 2017).

The single-center, open-label prospective ERICA study is ongoing at NPC to investigate the effect of alcohol consumption on retinal function, met the requirements of the Helsinki Declaration and was approved by the Ethics Committee of Bron-Sud Est II.

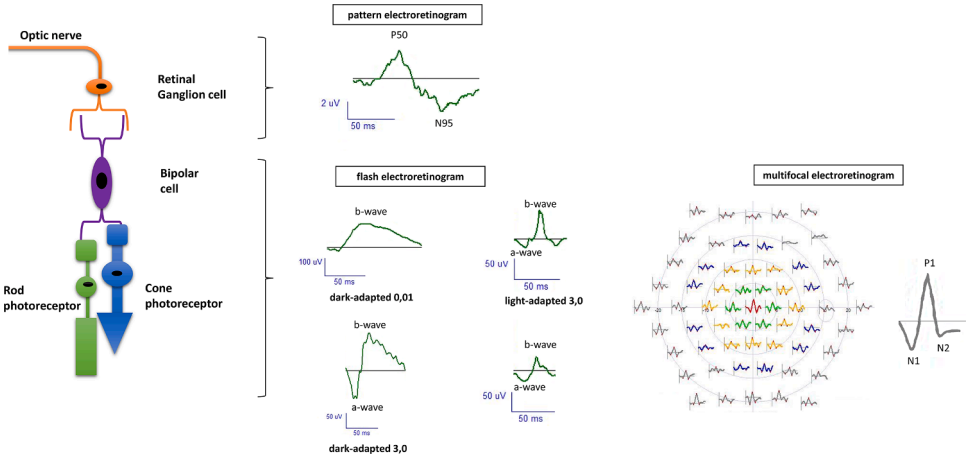

Fig. 1. Schematic representation of the retina and electroretinogram (ERG) traces.

2.2. Inclusion and exclusion criteria

2.2.1. Participants with MDD

The inclusion criteria for the participants with MDD were: an actual diagnosis of MDD in acute phase according to the Diagnostic and Statistical Manual *of Mental Disorders I-V* (DSM-IV), assessed by means of the Mini Neuropsychiatric International Interview (MINI) (Sheehan et al., 1998) and age between 18 and 60 years. The exclusion criteria were: a diagnosis of a progressive psychiatric disorder (other than MDD and anxiety disorder) according to Axis I of the DSM-IV, assessed by means of the MINI; seasonal affective disorder; a high suicide risk; an absence of routine care for MDD; previous or current light therapy treatment; an ongoing neurological disease and a retinal pathology.

2.2.2. Healthy controls

Healthy controls had no psychiatric disorder according to the DSM-IV assessed by means of the MINI (Sheehan et al., 1998), no ongoing neurological disease and no retinal pathology.

2.2.3. All participants

All participants underwent an ophthalmic evaluation including visual acuity measurement and a fundoscopic examination. Their visual acuity had to be at least 10/10 with optic correction in each eye measured with the Monoyer scale, and the fundoscopic examination had to be normal.

2.3. Assessment for participants with MDD

At baseline, the duration of the disease and current treatments were captured. Disease severity was estimated using the Montgomery-Åsberg Depression Rating Scale (MADRS) score (Montgomery and Asberg, 1979). Anxiety was estimated using the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959).

2.4. Experimental protocol for functional retinal assessment

The experimental protocol for functional retinal assessment was exactly the same in the LUMIDEP, CAUSAMAP and ERICA studies. Retinal data included in this report for the LUMIDEP study were recorded at baseline before the start of active or placebo light-therapy.

Pattern ERG (PERG), flash ERG (fERG) and multifocal ERG (mfERG) were performed according to the standards of the International Society for Clinical Electrophysiology of Vision (ISCEV) (Bach et al., 2013; Hoffmann et al., 2021; McCulloch et al., 2015; Robson et al., 2018). The MonPackOne system was used for the stimulation, the recording and the analysis. Both eyes were recorded simultaneously except for the mfERG, where each eye was recorded separately. Dawson-Trick-Litzkow (DTL) electrodes (Metrovision, Pérenchies, France) were placed at the bottom of the conjunctival sac, and ground and reference electrodes were attached to the forehead and external canthi. For the PERG measurements, the stimulus was a black and white contrast reversible checkerboard, with 0.8° check size, 93.3% contrast level, 100 cd/m^2 constant luminance white area, and 4 reversals per second. There are two principal segments in a typical PERG trace (Fig. 1): P50, an electropositive wave, that reflects the macular function, followed by N95, which is electronegative and reflects the function of the retinal ganglion cells (Bach et al., 2013). Dark-adapted 0.01 fERG and dark-adapted 3.0 fERG were performed after 20 min of dark adaptation. The stimulus in each case was a flash with a strength of 0.01 and 3.0 candela.m^2.s $^{-1}$, respectively. Then, after 10 min of light adaptation with a light background set at 30 cd/m^2 managed by the MonPackOne system, light-adapted 3.0 fERG and light-adapted 3.0 flicker fERG were recorded. The stimulus was a flash with a strength of 3.0 candela.m^2.s $^{-1}$. There are two main components on a fERG trace (Fig. 1): an electronegative component, the a-wave, followed by an electropositive component, the b-wave; in the case of the dark-adapted 0.01, however, the a-wave is masked by the b-wave. The a-wave reflects photoreceptors activity. Depending on the lighting environment and the flash intensity, the cones or the rods are preferentially recorded. The b-wave reflects the activity of bipolar cells (McCulloch et al., 2015). For the mfERG measurements, stimulation was a set of 61 scaled hexagons, corresponding to the central 20°, modulated between white and black in a pseudo-random sequence. mfERG signals were averaged over 5 retinal regions: ⟨2°, 2–5°, 5–10°, 10–15° and ⟩ 15° A typical mfERG trace is composed of an electronegative wave, N1, followed by an electropositive wave, P1, and lastly an electronegative wave, N2 (Hood et al., 2012) (Fig. 1). Two parameters are derived from each wave: the amplitude measured in μV and the peak time measured in ms. More details on ERG measurements are given in supplementary material 1 Data were analyzed with Ophthalmic Monitor (Metrovision, France). Averaged retinal responses were first obtained from each eye and then parameter, peak time and amplitude values, were averaged over both eyes for analysis.

2.5. Statistical analysis

All parameters were described by% for categorical variables and by median (Q1; Q3) for continuous variables.

Next, due to group matching, the McNemar test for categorial variables and the Wilcoxon signed ranks test for continuous variables were used when appropriate to compare variables in the group with MDD with those in the control group.

Finally, a receiver operating characteristic curve (ROC) was produced for the variables that differed between groups. If the area under the curve was > 0.8, the Youden index was calculated to determine the threshold value with the higher Youden index, so as to dichotomize the variables of interest according to this threshold, and to calculate the associated sensitivity and specificity values and their 95% confidence limits.

The significance threshold was set at 5%. Statistical analysis was performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Sample description

The demographic characteristics of the participants are described in Table 1. The median duration of the MDD was 225 days (Q1: 120; Q3: 365). Four patients had no previous MDD, four patients had one previous episode, three patients had two previous episodes and three patients had three or more previous episodes. Of the 14 patients, 13 were

Table 1
demographic characteristics (%/median, 1st and 3rd quartiles).

	Patients with MDD (n = 14)	Controls (n = 14)	p-value
Gender (% male/female)	42.9/57.1	42.9/57.1	1
Age (years)	32.5 [30; 40]	32.5 [28; 35]	0.09
Education (years)	14 [12; 15]	15 [14; 16]	0.012
AUDIT	4 [2; 11]	2.5 [1; 4]	0.08
Alcohol use (glass/week)	1.5 [0; 5]	1.5 [0; 4]	0.58
Tobacco use (cigarettes/day)	6 [0; 15]	6 [0; 17]	0.35
Tobacco use (pack-year) [a]	1.3 [0; 7.5]	9.8 [4.6; 18.4]	0.06
Fagerström test	1.5 [0; 5]	5.0 [3.5; 8.5]	0.63
MARDS score	27.5 [18; 34]	–	–
MADRS self-assessment score	13 [11.5; 18.5]	–	–
Hamilton	14 [12; 16]	–	–

McNemar test for categorial variables and Wilcoxon signed ranks test for continuous variables (matched sample).
[a] data available for the 8 smoker participants in the control group.

receiving antidepressant treatment, with two patients using a combination of two antidepressants. Seven patients were on a Selective serotonin reuptake inhibitor (SSRI), six on a Serotonin and norepinephrine reuptake inhibitor (SNRI), one on a tricyclic and one on mirtazapine. Nine patients had a benzodiazepine prescription, two an anti-histamine, three a hypnotic, four antipsychotics and one a mood stabilizer. Additionally, three patients were on non-psychotropic treatments.

3.2. ERG parameters

Table 2 and Fig. 2 summarize all the results for the PERG, fERG and mfERG measurements. Only significant results are included in the following paragraphs.

3.3. PERG parameters: N95 and P50

The P50 peak time was increased by approximately 1 ms in MDD group compared to control group ($p = 0.005$).

3.4. fERG parameters

3.4.1. Dark-adapted 3.0 fERG

The a-wave peak time median was lower of approximatively 8 ms in MDD group compared to control group ($p = 0.03$).

The b-wave peak time median was decreased by approximatively 8 ms MDD group compared to control group (p = 0,03). The b-wave amplitude median was higher of approximatively 46 μV in MDD group compared to control group ($p = 0.003$).

3.4.2. Light-adapted 3.0 fERG

The a-wave peak time was decreased by approximately 4 ms in MDD group compared to control group ($p = 0.0005$). The a-wave amplitude was increased by approximately 8 μV in MDD group compared to control group ($p = 0.001$).

The b-wave peak time was decreased by approximately 6 ms in MDD group compared to control group ($p = 0.0002$). The b-wave amplitude was increased by approximately 34 μV in MDD group compared to control group ($p = 0.0005$) (Fig. 3).

3.4.3. Light-adapted flicker fERG

The b-wave peak time was decreased by approximately 2 ms in MDD group compared to control group ($p = 0.0005$).

3.5. mfERG

In ring 2 (2–5°): the P1 amplitude was decreased by approximately 90 μV in MDD group compared to control group ($p = 0.005$) (Fig. 4).

In ring 3 (10–15°): the N1 peak time was increased by approximately 1 ms in MDD group compared to control group ($p = 0.010$).

3.6. Cut-off values

ROC curves were built to identify the optimal cut-off values of variables that differed significantly between groups. Cut-off values, sensitivity, specificity, positive predictive values and negative predictive values are shown in Table 3.

The area under the curve was 0.69 and 0.51 for the mfERG P1 amplitude in ring 2 and the P50 peak time respectively, so that no threshold value was searched.

4. Discussion

This was the first study to assess whole retina function using PERG, fERG and mfERG according to the ISCEV standardized protocol in patients with non-seasonal MDD in acute phase, compared with healthy controls. Firstly, our results indicate delayed retinal signaling in the

Table 2
Electroretinogram (ERG) parameters of the participants.

	MDD patients ($n = 14$) Median (Q1; Q3)	Controls ($n = 14$) Median (Q1; Q3)	p-value [a]
Pattern electroretinogram (PERG)			
P50 peak Time (ms) [c]	**51.1 (48.6 ; 52.2)**	**50.2 (48.8. 54.9)**	**0.005**
P50 Amplitude (μV) [c]	2.2 (1.7 ; 2.5)	2.9 (2.3 ; 3.3)	0.583
N95 peak time (ms) [c]	95.9 (91.8 ;99.2)	92.7 (87.6 ; 97.5)	0.301
N95 amplitude (μV) [c]	−3.1 (−3.7 ; −2.6)	−2.0 (−2.9 ; 1.2)	0.147
Flash electroretinogram (fERG)			
– Dark-adapted 0.01 ERG			
b-wave peak time (ms) [b]	76.9 (68.5 ; 82.6)	79.5 (78.5 ; 84.4)	0.339
b-wave amplitude (μV) [b]	122.0 (103.3 ; 143.5)	118.5 (100.3 ; 139.0)	0.735
Dark-adapted 3.0 ERG			
a-wave peak time (ms) [c]	**16.3 (15.8 ; 20.9)**	**24.6 (24.1;25.0)**	**0.033**
a-wave amplitude (μV) [c]	−126.5 (−136.5; −86.5)	−82.6 (−104.5 ; −66.8)	0.233
b-wave peak time (ms) [c]	**39.3 (38.6 ; 40.8)**	**47.1 (46.0 ; 47.3)**	**0.033**
b-wave amplitude (μV) [c]	**202.3 (170.3 ; 228.8)**	**156.3 (118.8 ; 168.3)**	**0.003**
– Light-adapted 3.0 ERG			
a-wave peak time (ms) [b]	**14.9 (14.9 ; 15.3)**	**18.6 (18.1 ; 19.5)**	**0.0005**
a-wave amplitude (μV) [b]	**−17.6 (−20.0 ; −14.1)**	**−9.3 (−12.5 ; −7.8)**	**0.001**
b-wave peak time (ms) [b]	**30.0 (29.5 ; 30.0)**	**36.3 (35.4 ; 37.2)**	**0.0002**
b-wave amplitude (μV) [b]	**81.8 (78.5 ; 87.2)**	**47.6 (39.3 ; 50.7)**	**0.0005**
– Light-adapted Flicker 3.0			
a-wave peak time (ms) [c]	14.6 (14.2 ; 17.0)	15.9 (15.3 ; 17.0)	0.378
a-wave amplitude (μV) [c]	−36.9 (−45.6 ; −29.8)	−40.3 (−56.6 ; −27.5)	0.569
b-wave peak time (ms) [c]	**27.8 (27.2 ; 28.3)**	**29.9 (29.2 ; 30.1)**	**0.0005**
b-wave amplitude (μV) [c]	69.9 (50.8 ; 89.9)	59.3 (44.7 ; 78.8)	0.151
Multifocal electroretinogram (mfERG)			
< 2° (ring 1)			
N1 amplitude (μV) [c]	−432.8 (−534.5 ; −331.3)	−574.5 (−761.0 ; −425.5)	0.23
N1 peak time (ms) [c]	25.9 (24.9 ; 28.4)	27.4 (25.5 ; 28.5)	0.27
P1 amplitude (μV) [c]	867.0 (704.0 ; 1.066.5)	978.5 (780.5 ; 1.175.5)	0.30
P1 peak time (ms) [c]	50.3 (48.4 ; 51.0)	51.1 (49.7 ; 53.1)	0.18
N2 amplitude (μV) [c]	−896.0 (−973.8 ; −730.8)	−964.8 (−1.140.0 ; −705.5)	0.47
N2 peak time (ms) [c]	72.6 (70.6 ; 73.0)	72.4 (71.2 ; 74.3)	0.20
2–5° (ring 2)			
N1 amplitude (μV) [c]	−185.8 (−260.5 ; −159.5)	−240.0 (−301.8 ; −215.0)	0.09
N1 peak time (ms) [c]	26.0 (25.3 ; 28.1)	25.7 (24.4 ; 27.0)	0.29
P1 amplitude (μV) [c]	**409.3 (375.5 ; 459.0)**	**498.3 (460.3 ; 549.3)**	**0.005**
P1 peak time (ms) [c]	45.8 (45.4 ; 46.9	45.7 (44.4 ; 46.5	0.21
N2 amplitude (μV) [c]	−399.5 (−424.0 ; −266.3)	−424.3 (−457.8 ; −351.8)	0.85
N2 peak time (ms) [c]	66.4 (64.6 ; 69.5)	68.1 (66.1 ; 72.2)	0.52
5–10° (ring 3)			
N1 amplitude (μV) [c]	−184.8 (−216.9 ; −138.7)	−223.5 (−245.3 ; −192.3)	0.23

(*continued on next page*)

Table 2 (*continued*)

	MDD patients ($n = 14$) Median (Q1; Q3)	Controls ($n = 14$) Median (Q1; Q3)	p-value [a]
N1 peak time (ms) [c]	**25.1 (24.1 ; 26.2)**	**24.3 (23.6 ; 24.9)**	**0.01**
P1 amplitude (μV) [c]	345.8 (300.6 ; 368.8)	389.8 (337.5 ; 445.0)	0.11
P1 peak time (ms) [c]	42.7 (42.1 ; 44.0)	43.3 (42.6 ; 43.8)	0.85
N2 amplitude (μV) [c]	−314.8 (−373.5 ; −274.2)	−340.0 (−367.8 ; −289.5)	0.38
N2 peak time (ms) [c]	61.5 (61.0 ; 66.2)	62.2 (61.4 ; 65.7)	0.79
10–15° (ring 4)			
N1 amplitude (μV) [c]	−162.8 (−204.3 ; −111.5)	−166.5 (−196.5 ; −141.5)	0.23
N1 peak time (ms) [c]	25.2 (24.1 ; 26.0)	24.3 (23.6 ; 25.4)	0.21
P1 amplitude (μV) [c]	349.5 (336.3 ; 393.5)	356.8 (300.3 ; 413.3)	0.85
P1 peak time (ms) [c]	43.2 (42.1 ; 44.5)	42.8 (42.3 ; 43.7)	0.63
N2 amplitude (μV) [c]	−308.0 (−358.8 ; −273.5)	−307.5 (−383.8 ; −261.0)	1.00
N2 peak time (ms) [c]	61.5 (60.4 ; 66.3)	60.9 (60.1 ; 62.4)	0.13
> 15° (ring 5)			
N1 amplitude (μV) [c]	−166.0 (−204.8 ; −154.8)	−143.5 (−190.0 ; −111.3)	0.30
N1 peak time (ms) [c]	24.8 (23.6 ; 25.1)	24.3 (24.1 ; 24.8)	0.91
P1 amplitude (μV) [c]	350.0 (317.3 ; 420.0)	348.3 (304.3 ; 395.8)	0.73
P1 peak time (ms) [c]	42.7 (42.0 ; 43.6)	42.4 (42.1 ; 42.9)	0.81
N2 amplitude (μV) [c]	−305.8 (−340.3 ; −289.3)	−306.8 (−359.0 ; −285.8)	0.86
N2 peak time (ms) [c]	61.1 (60.1 ; 62.8)	60.4 (59.9 ; 61.8)	0.37

Variable represented as median, 1st and 3rd quartiles.
[a] Wilcoxon Signed Rank Test for continuous variables.
[b] data missing for 1 participant.
[c] data missing for 2 participants.

central retina in patients with MDD. Indeed, in the cone system in mfERG, the N1 peak time in ring 3 was increased by about 1 ms and the P1 amplitude in ring 2 was decreased by about 90 μV. Moreover, delayed macular function was also apparent on the PERG in the form of an increase of about 1 ms in P50 peak time. Secondly, in the fERG global retina recording we observed hyperactivity of the peripheral retina. In fact, compared with the controls, in the dark-adapted 3.0 we observed a decrease in a- and b-wave peak time of about 8 ms, with an increase in b-wave amplitude of about 46 μV; in the light-adapted 3.0, a decrease in a- and b-wave peak time of about 4 and 6 ms respectively, with an increase in both wave amplitudes; and in the light-adapted flicker, a decrease of about 2 ms in the b-wave peak time.

In the central retina we found delayed retinal signaling in patients with MDD compared with the controls. mfERG examines the local properties of central retinal cone system function. The mfERG responses were averaged over five retinal regions: <2°, 2°–5°, 5°–10°, 10°–15° and >15° (Fig. 1). On a mfERG trace, N1 reflects the hyperpolarization of the OFF cone bipolar cells and P1 the depolarization of the ON cone bipolar cells (Holder et al., 2010). Our results thus indicate hyporeactivity to light in the OFF cone bipolar cells and a decrease in the number of ON bipolar cells recruited in the central retina, i.e., a dysfunction of the central retina. This is consistent with our findings with PERG, reflecting the macular function of the retina. There was an increase in P50 peak time in the MDD group compared with the healthy controls, with no abnormality in the N95 wave. Both P50 and N95 waves originate from the macular ganglion cells but with a major contribution from the distal retina to the P50 wave (Robson et al., 2018). In the macula, therefore, the photoreceptor and bipolar cell stages have delayed function, whereas the ganglion cell stage appears unaffected. In summary, our results indicate delayed function of the photoreceptor and bipolar cell stages in the central retina. Cones are numerous and densely packed in the central retina. Their number decrease from the center to the retinal periphery (Curcio et al., 1990). They are responsible for color vision, contrast sensitivity and accurate vision (Stewart et al., 2020). In contrast, rods are absent in the fovea and abundant in the periphery (Curcio et al., 1990). Peripheral vision is less precise and less sensitive to contrast but allows for a large visual field (Stewart et al., 2020). Furthermore, in the central retina cones converge almost one-to-one on a single retinal ganglion cell, whereas in the periphery there are many photoreceptors converging to a retinal ganglion cell (Curcio and Allen, 1990), leading to an over-representation of the central retina throughout visual pathways (Horton and Hoyt, 1991). Interestingly, it had already been reported that patients with MDD were more likely to perceive the light in their surroundings as being dimmer than it normally appears. In the same way, people who reported dimness were 4.5 times more likely to report symptoms of MDD (Friberg et al., 2008). We can therefore assume that a slowdown in the central retina might contribute to this impression. The slowdown is also apparent at other levels in MDD. In fact, a slowing-down of thought and a reduction in physical movement are part of the clinical criteria for diagnosis (American Psychiatric Association, 2013). At the cognitive level, people with MDD may experience cognitive deficits in executive function, memory and attention (Rock et al., 2014). As stated above, P50 reflects the macular function of the global retinal layers and we may ask whether this wave could be a marker of physical and cognitive slowdown in MDD.

We also found that MDD has an impact on global retina function recorded with the fERG. On a fERG trace, the a-wave reflects the function of the photoreceptors and the b-wave that of the bipolar cells. In the dark-adapted 3.0, representing the mixed rod/cone system, we observed a decrease in a- and b-wave peak times, with an increase in b-wave amplitude in MDD patients compared with healthy controls. In the light-adapted 3.0, reflecting cone system responses, there was a decrease in a- and b-wave peak times, with an increase in both wave amplitudes. There was also a decrease in the b-wave peak time in the light-adapted flicker, reflecting the function of the cone bipolar cells. Conversely, there was no change in the dark-adapted 0.01 representing the rod system response. In the photoreceptors, therefore, these data suggest hyperreactivity to light mainly in the cones. The number of cones recruited is also increased, whereas there is no change in the number of rods recruited. As regards the bipolar cells, both ON and OFF cone bipolar cells and rod bipolar cells are hyperreactive and the number of cells recruited is increased. In contrast to the central retina, therefore, which is hypoactive, the peripheral retina is hyperactive. We can hypothesize that the peripheral retina compensates for the hypoactivation of the central retina by being hyperactivated. It remains to be determined whether this hyperactivation is related only to MDD or to the treatment, and whether this hyperactivation is functional or not. At a higher cortical level, visual process has also been found to be altered. Indeed, patients with MDD had different contrast sensitivity from controls (Bubl et al., 2009; Fam et al., 2013; Nogueira et al., 2013; Wesner and Tan, 2006). For example, Wesner et al. found that patients with MDD showed enhanced contrast sensitivity in static high frequency (Wesner and Tan, 2006). Bubl et al. showed a highly significant increase in contrast discrimination thresholds in medicated and unmedicated patients with MDD, corresponding to a 15% increase over the mean thresholds of the control group (Bubl et al., 2009); this is consistent with Fam's results, who also found a correlation between greater severity of MDD and poorer contrast discrimination (Fam et al., 2013). The relationship between low and high visual process during MDD is not currently explained, but interestingly, in addition to retinal function Bubl et al. also assessed visual evoked potential and their results suggest a correlation between retinal and cortical response (Bubl et al., 2015). It can therefore be assumed

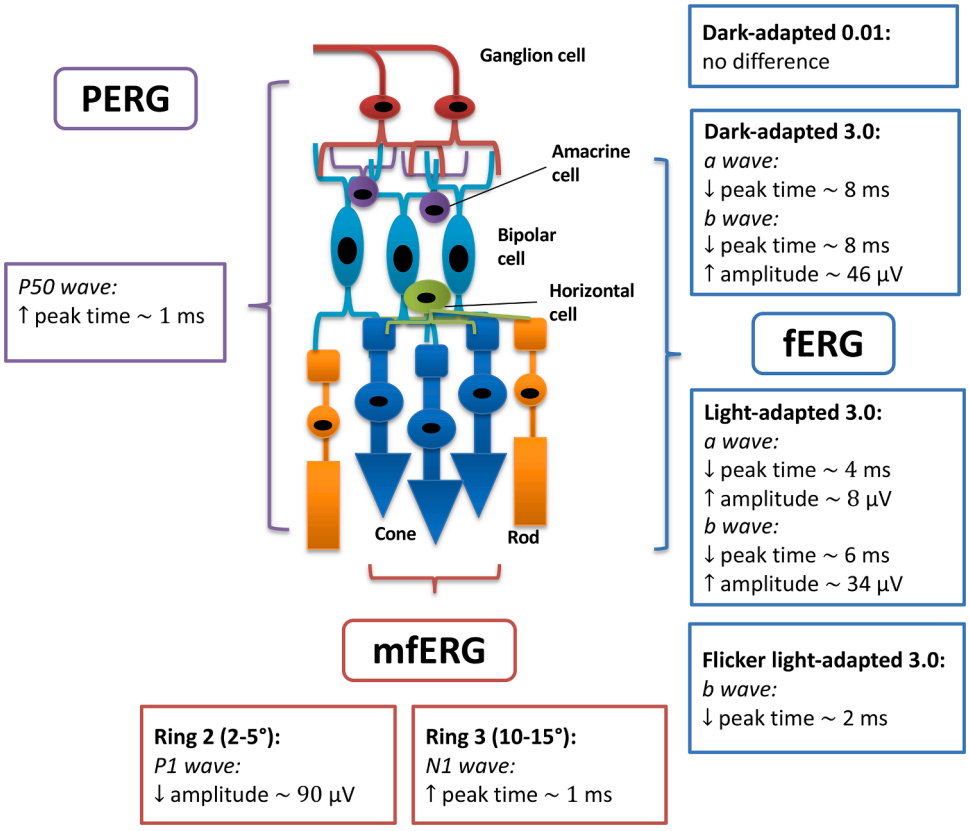

Fig. 2. Schematic representation of the retina and summary of our results.

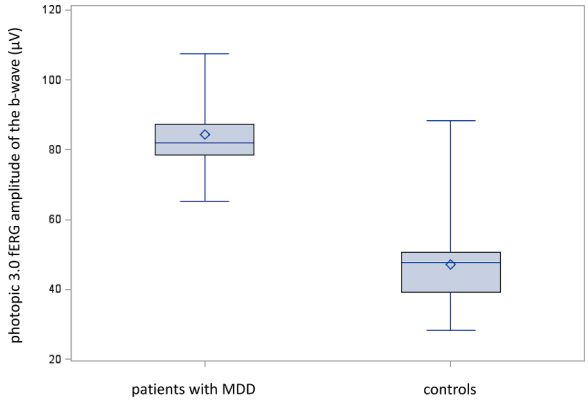

Fig. 3. Box plot of photopic 3.0 flash electroretinogram (fERG) b-wave amplitude (µV) for patient with MDD and controls. Patients with MDE exhibit increased amplitude and the difference between groups is significant (p = 0.0005: Wilcoxon signed rank test on Matched Samples).

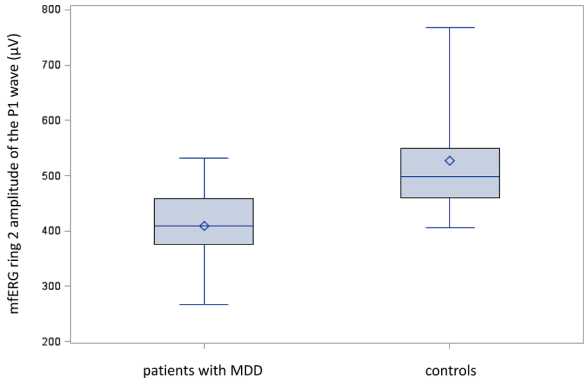

Fig. 4. Box plot of ring 2 multi focal electroretinogram (mfERG) P1 wave amplitude (µV) for patient with MDD and controls. Patients with MDE exhibit decreased amplitude and the difference between groups is significant (p = 0.005: Wilcoxon signed rank test on Matched Samples).

that the various functional retinal processes may reflect various pathophysiological processes of MDD occurring in the cortex.

Abnormalities of retinal function in patients with MDD have already been reported in some but not all studies. No previous study has used mfERG to investigate central retinal function. However, regarding ganglion cells layer, Fam et al.'s results, like ours, indicate no deterioration in this retinal layer in MDD (Fam et al., 2013). Bubl et al. reported conflicting results (Bubl et al., 2010) but indicating of macular hypofunction of the retina, which we highlighted in the other layers of the retina. In whole retina recording, Hébert et al. (Hébert et al., 2017) also found abnormalities in the cone and mixed rod/cone pathway but with increased cone and mixed rod/cone b-wave peak times and decreased mixed rod/cone a- and b-wave amplitudes in patients with MDD compared with controls (Hébert et al., 2017). Like us, Fam et al. found no deterioration in the scotopic rod fERG (Fam et al., 2013). However, they found no deterioration in the mixed rod/cone pathways (Fam et al., 2013). Fornaro et al. also reported negative findings (Fornaro et al., 2011). Demmin et al. found ganglion cell dysfunction, and no dysfunction in photoreceptors and bipolar cells (Demmin et al., 2020).

It is crucial to ask why the results are contrasting. When looking at the ERG techniques used in the different studies, a number of methodological differences can be highlighted. First, participant preparation varies across studies. Indeed, to record retinal signals, some studies used DTL electrodes (Bubl et al., 2010; Fam et al., 2013; Hébert et al., 2017), i.e., electrodes placed at the bottom of the conjunctival sac, in direct contact with the cornea, whereas others used skin electrodes (Demmin

Table 3
Cut-off value to discriminate controls and patients with MDD.

	Cut-off value	Sensibility	Specificity	Positive predictive value	Negative predictive value
dark-adapted 3.0 fERG					
a-wave peak time	21.534 ms	83.3% [68.4%–98.2%]	100% [100%–100%]	100% [100%–100%]	85.7% [71.7%–99.7%]
b-wave peak time	41.503 ms	91.7% [80.6%–100%]	100% [100%–100%]	100% [100%–100%]	92.0% [81.1%–100%]
b-wave amplitude	172.958 µV	75% [57.7%–92.3%]	83.3% [68.4%–98.2%]	81.8% [66.4%–97.2%]	76.9% [60%–93.8%]
light-adapted 3.0 fERG					
a-wave peak time	15.799 ms	84.6% [70.2%–99.0%]	92.3% [81.6%–100%]	91.7% [80.7%–100%]	85.7% [71.7%–99.7%]
a-wave amplitude	−13.350 µV	76.9% [60.0%–93.8%]	100% [100%–100%]	100% [100%–100%]	81.2% [65.6%–96.8%]
b-wave peak time	32.598 ms	76.9% [60.0%–93.8%]	100% [100%–100%]	100% [100%–100%]	81.2% [65.6%–96.8%]
b-wave amplitude	65.352 µV	92.3% [81.6%–100%]	92.3% [81.6%–100%]	92.3% [81.6%–100%]	92.3% [81.6%–100%]
light-adapted flicker fERG					
b-wave peak time	28.300 ms	91.7% [80.7%–100%]	100% [100%–100%]	100% [100%–100%]	92.3% [81.6%–100%]
mfERG					
ring 3 N1 peak time	425.895 ms	58.3% [38.6%–78.0%]	91.7% [80.7%–100%]	87.5% [74.3%–100%]	68.7% [50.1%–87.3%]

et al., 2020; Fornaro et al., 2011), which have been shown to provide lower amplitude and higher electrical noise during recording (Fernandes et al., 2016). Similarly, pupils were dilated in some studies (Fam et al., 2013; Fornaro et al., 2011), but not in others (Demmin et al., 2020; Hébert et al., 2017), which influences ERG recordings (Gagné et al., 2010). Moreover, the dark adaptation time before scotopic recording and the light adaptation time before photopic recording vary across studies (Demmin et al., 2020; Fornaro et al., 2011; Hébert et al., 2017). Secondly, retinal stimuli vary across studies. Thus, for recording PERG contrast gain, Bubl et al. and Fam et al's studies differed in the contrast levels of the stimuli. Stimuli for rod system recording in global retinal function recording were either a dim white flash of 0.01 cd.s/m^2 (Fam et al., 2013; Fornaro et al., 2011) or a green flash of 0.1 cd.s/m^2 (Hébert et al., 2017), and for the mixed rod/cone system, either a white flash of 3.0 cd.s/m^2 (Fam et al., 2013; Fornaro et al., 2011) or a green flash of 1.0 cd.s/m^2 (Hébert et al., 2017). Stimulation also varied for the cone system recording. Stimuli were either a flash of 3.0 cd.s/m^2 with a background of 30 cd.s/m^2 (Fornaro et al., 2011), or 12 white flashes ranging from 0.75 cd.s/m^2 to 800 cd.s/m^2 (Hébert et al., 2017), or stimulus with dynamic adaptation of light intensity (Demmin et al., 2020). The strength of the stimulus, its wavelength and background illumination affect the responses of the different retinal cells and impact the electroretinogram (Frishman, 2018). To conclude, protocols for retinal assessment vary considerably across studies leading to divergent results, making it difficult to draw comparisons between studies. To overcome these issues we chose to assess retinal function with a standardized, reproducible protocol defined by the ISCEV.

4.1. Limitations

This study has some limitations. First, the sample size is limited, but we were able to find statistically significant differences. The size of the study may not have allowed us to reveal other differences due to a lack of power, so recruitment is continuing to confirm the results in a larger population and to follow the evolution of retinal function during MDD. Second, the study has a naturalistic design, so we did not control for pharmacological treatments. Contribution of pharmacological treatments to the outcomes cannot be formally excluded. To our knowledge, very few studies have assessed the impact of medication alone on human ERG. In healthy volunteers, no effect of a single dose of tricyclic antidepressant on the rod pathway was found (Perossini and Fornaro, 1990), whereas a single dose of agomelatine, a melatoninergic antidepressant, induced a slight increase in cone b-wave amplitude and latency within the normal variation of the measure (Fornaro et al., 2014). Twelve weeks of treatment with an SNRI did not result in any change in the rod and mixed rod/cone response in a group of healthy volunteers (Fornaro et al., 2011). In our study, patients were on antidepressants and on other psychopharmacological treatment. With benzodiazepine, no change in the rods was recorded on the electroretinogram after a single intake of diazepam (Perossini and Fornaro, 1990), whereas oxazepam induced an isolated decrease in rod b-wave peak time (Bartel et al., 1990). However, the pharmacological effect of single-dose intake varies from that of regular treatment or a combination of treatments. In Bubl's study, half of the patients were medicated and half unmedicated. Both groups showed reduced contrast gain (Bubl et al., 2010). The authors found no effect of intensity of antidepressant treatment or of its pharmacological classes. There is nevertheless a need for a better understanding of the impact of medication on ERG.

Finally, it has already been demonstrated that use of substances (Lavoie et al., 2014b) such as cannabis (Lucas et al., 2019; Schwitzer et al., 2018, 2017, 2020) impacts retinal function; for this reason, addictive comorbidities or substance use were exclusion criteria. However, substance use may be associated with MDD (Hasin et al., 2018; Holma et al., 2020; Hunt et al., 2020; Pacek et al., 2013). Retinal abnormalities in patients with both MDD and substance use disorders therefore remain to be specified. Moreover, tobacco is another substance that might impact retinal function (Gundogan et al., 2007; Varghese et al., 2011), but because of its widespread nature, tobacco use was not an exclusion criterion. There was no difference between the two groups in terms of actual tobacco consumption. Finally, both groups differed in terms of educational level but this was not integrated into the statistical analysis as it has no impact on retinal function.

4.2. Perspectives

Our results further indicate that ERG, and especially fERG, could be a relevant tool to enhance diagnosis of MDD. Indeed, of the cut-off values determined with ROC curves to distinguish patients from controls, the b-wave peak times in the dark-adapted ERG have a sensitivity of 91.7% and a specificity of 100%. It is also crucial to distinguish MDD from other psychiatric disorders. This is especially true for bipolar disorder. In fact, bipolar disorder frequently begins with a depressive episode and hypomanic episodes may not be noticed (Angst et al., 2011; Solomon et al., 2006). Misdiagnosing a bipolar depressive episode as a unipolar

depressive episode leads to inappropriate treatment with a risk of rapid cycling, poorer outcomes, more severe symptoms and impaired psychosocial functioning (Hirschfeld et al., 2003; Nivoli et al., 2011; Solomon et al., 2006). It is therefore critical to be able to distinguish bipolar from unipolar depressive episodes at an early stage. We believe that retinal assessment might be a relevant tool to distinguish psychiatric pathologies. Future studies should explore the differences between the retinal function of patients with unipolar and those with bipolar disorder.

Clinicians also lack objective tools to monitor MDD progression, confirm remission, detect a relapse at an early stage or predict the future effectiveness of treatment. Studies have already suggested that ERG might be relevant for these purposes (Bubl et al., 2012; Fornaro et al., 2011). Further investigation is required to confirm this and determine the points at which the electroretinographic changes appear. Furthermore, there is a need to specify for which treatments the study of the retina can effectively predict the outcome. This applies to pharmacological treatments as well as non-pharmacological treatment, such as light therapy, which has been shown to be effective in MDD (Geoffroy et al., 2019). It is crucial in the future to assess whether ERG can be an early marker of relapse. Moreover, it would be interesting to combine ERG markers with other markers. Finally, MDD is a heterogenous disease defined only by clinical symptomatology. It would be relevant in the future to use ERG to try to identify homogeneous patient subgroups based on the underlying pathophysiology.

5. Conclusion

This study was the first to evaluate the global and local properties of retinal function with reproducible standardized PERG, fERG and mfERG according to the ISCEV protocol in patients with MDD in acute phase compared with healthy controls. Our results indicate abnormalities in the function of the cones system in the central retina, as well as dysfunctions in the photoreceptors and the bipolar cells during the recording of global retinal function. MDD is a common and debilitating disease. The assessment of the functional properties of the retina could be a tool to help in the diagnosis, the choice of treatment, the monitoring of the evolution of the disease and the early detection of relapses. In addition, the advantage is that ERG is a straightforward, non-invasive, no-cost procedure that is quick to perform. The use of a standardized protocol allows for replication. However, there is still a need to interpret the plots. Artificial intelligence has developed over the last few years, though, and in the future, this could be a promising approach for interpreting data and assessing differences in PERG, fERG and mfERG between patients and controls.

Author statement

Contributors

EC contributed to the study design, literature search, data acquisition and interpretation and wrote the initial version of the manuscript with support from TS.

TS contributed to gaining funding for the current study, to the study design, the literature search, the interpretation of the data and to the writing of the manuscript.

MM contributed to data acquisition and to the writing of the manuscript.

CB contributed to the design of the data analysis for the study. CB and AL contributed to analysis plan, performed statistical analysis and contributed to the methodological and results section of the manuscript.

KA-D contributed to the ancillary part of the study, to ophthalmologic data acquisition and interpretation and to the critically revision of the manuscript.

RS and VL contributed to the development of the research question and to the critically revision of the manuscript.

All authors read, critically revised and approved the final version of the manuscript.

Role of the funding source

This work was supported by the Nancy Psychotherapeutic Center, France and LUCIMED SA, Belgium. The funders did not influence the design of the study, the collection, management, analysis and interpretation of the data, the writing of the report or the decision to submit the report for publication. They do not have authority over any of these activities.

Ethical statement

The study protocol met the requirements of the Helsinki Declaration and was approved by Ile-de France X's Ethics Committee (protocol number 34–2018) and the trial is registered at clinicaltrials.gov: NCT03685942; September 26, 2018. https://clinicaltrials.gov/ct2/show/NCT03685942.

Declaration of Competing Interest

The authors report no biomedical financial interests or potential conflicts of interest.

Acknowledgments

We would like to thank all the patients who kindly participate in this study and all the members who contributed to the LUMIDEP study group : Ambre Leguay, Héloïse Vinsard, Gaëlle Zeck, Clarisse Bugin, Damien Frigi and Jean Drogo. We also thank the ophthalmology staff of Nancy University Hospital for their contribution to this work.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.08.054.

References

American Psychiatric Association, American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental disorders: DSM-5, 5th ed. ed. American Psychiatric Association, Washington, D.C.

Angst, J., Azorin, J.-.M., Bowden, C.L., Perugi, G., Vieta, E., Gamma, A., Young, A.H., BRIDGE Study Group, 2011. Prevalence and characteristics of undiagnosed bipolar disorders in patients with a major depressive episode: the BRIDGE study. Arch. Gen. Psychiatry 68, 791–798. https://doi.org/10.1001/archgenpsychiatry.2011.87.

Bach, M., Brigell, M.G., Hawlina, M., Holder, G.E., Johnson, M.A., McCulloch, D.L., Meigen, T., Viswanathan, S., 2013. ISCEV standard for clinical pattern electroretinography (PERG): 2012 update. Doc. Ophthalmol. Adv. Ophthalmol. 126, 1–7. https://doi.org/10.1007/s10633-012-9353-y.

Bartel, P., Blom, M., Robinson, E., Van der Meyden, C., Sommers, D.O., Becker, P., 1990. Effects of chlorpromazine on pattern and flash ERGs and VEPs compared to oxazepam and to placebo in normal subjects. Electroencephalogr. Clin. Neurophysiol. 77, 330–339. https://doi.org/10.1016/0168-5597(90)90054-h.

Baylor, D., 1996. How photons start vision. Proc. Natl. Acad. Sci. U. S. A. 93, 560–565. https://doi.org/10.1073/pnas.93.2.560.

Bernardin, F., Schwitzer, T., Angioi-Duprez, K., Giersch, A., Jansen, C., Schwan, R., Laprevote, V., 2020. Retinal ganglion cells dysfunctions in schizophrenia patients with or without visual hallucinations. Schizophr. Res. 219, 47–55. https://doi.org/10.1016/j.schres.2019.07.007.

Bubl, E., Ebert, D., Kern, E., van Elst, L.T., Bach, M., 2012. Effect of antidepressive therapy on retinal contrast processing in depressive disorder. Br. J. Psychiatry J. Ment. Sci. 201, 151–158. https://doi.org/10.1192/bjp.bp.111.100560.

Bubl, E., Kern, E., Ebert, D., Bach, M., Tebartz van Elst, L., 2010. Seeing gray when feeling blue? depression can be measured in the eye of the diseased. Biol. Psychiatry 68, 205–208. https://doi.org/10.1016/j.biopsych.2010.02.009.

Bubl, E., Kern, E., Ebert, D., Riedel, A., Tebartz van Elst, L., Bach, M., 2015. Retinal dysfunction of contrast processing in major depression also apparent in cortical activity. Eur. Arch. Psychiatry Clin. Neurosci. 265, 343–350. https://doi.org/10.1007/s00406-014-0573-x.

Bubl, E., Tebartz Van Elst, L., Gondan, M., Ebert, D., Greenlee, M.W., 2009. Vision in depressive disorder. World J. Biol. Psychiatry Off. J. World Fed. Soc. Biol. Psychiatry 10, 377–384. https://doi.org/10.1080/15622970701513756.

Cosker, E., Moulard, M., Schmitt, S., Angioi-Duprez, K., Baumann, C., Laprévote, V., Schwan, R., Schwitzer, T., 2021. Portable light therapy in the treatment of unipolar non-seasonal major depressive disorder: study protocol for the LUMIDEP randomised controlled trial. BMJ Open. https://doi.org/10.1136/bmjopen-2021-049331.

Cosker, E., Schwan, R., Angioi-Duprez, K., Laprévote, V., Schwitzer, T., 2020. New insights on the role of the retina in diagnostic and therapeutic strategies in major depressive disorder. Neurosci. Biobehav. Rev. 113, 262–272. https://doi.org/10.1016/j.neubiorev.2020.03.006.

Curcio, C.A., Allen, K.A., 1990. Topography of ganglion cells in human retina. J. Comp. Neurol. 300, 5–25. https://doi.org/10.1002/cne.903000103.

Curcio, C.A., Sloan, K.R., Kalina, R.E., Hendrickson, A.E., 1990. Human photoreceptor topography. J. Comp. Neurol. 292, 497–523. https://doi.org/10.1002/cne.902920402.

de Souza, C.F., Acosta, M.L., Polkinghorne, P.J., McGhee, C.N.J., Kalloniatis, M., 2013. Amino acid immunoreactivity in normal human retina and after brachytherapy. Clin. Exp. Optom. 96, 504–507. https://doi.org/10.1111/cxo.12011.

Demmin, D.L., Netser, R., Roché, M.W., Thompson, J.L., Silverstein, S.M., 2020. People with current major depression resemble healthy controls on flash Electroretinogram indices associated with impairment in people with stabilized schizophrenia. Schizophr. Res. 219, 69–76. https://doi.org/10.1016/j.schres.2019.07.024.

Duman, R.S., Sanacora, G., Krystal, J.H., 2019. Altered connectivity in depression: GABA and glutamate neurotransmitter deficits and reversal by novel treatments. Neuron 102, 75–90. https://doi.org/10.1016/j.neuron.2019.03.013.

Fam, J., Rush, A.J., Haaland, B., Barbier, S., Luu, C., 2013. Visual contrast sensitivity in major depressive disorder. J. Psychosom. Res. 75, 83–86. https://doi.org/10.1016/j.jpsychores.2013.03.008.

Fernandes, A.G., Salomão, S.R., Pereira, J.M., Berezovsky, A., 2016. Full-field electroretinogram recorded with skin electrodes in normal adults. Arq. Bras. Oftalmol. 79, 390–394. https://doi.org/10.5935/0004-2749.20160110.

Fornaro, M., Bandini, F., Cestari, L., Cordano, C., Ogliastro, C., Albano, C., De Berardis, D., Martino, M., Escelsior, A., Rocchi, G., Fornaro, P., De Pasquale, C., 2014. Electroretinographic modifications induced by agomelatine: a novel avenue to the understanding of the claimed antidepressant effect of the drug? Neuropsychiatr. Dis. Treat. 10, 907–914. https://doi.org/10.2147/NDT.S63459.

Fornaro, M., Bandini, F., Ogliastro, C., Cordano, C., Martino, M., Cestari, L., Escelsior, A., Rocchi, G., Colicchio, S., Perugi, G., 2011. Electroretinographic assessment in major depressed patients receiving duloxetine: might differences between responders and non-responders indicate a differential biological background? J. Affect. Disord. 135, 154–159. https://doi.org/10.1016/j.jad.2011.07.013.

Friberg, T.R., Bremer, R.W., Dickinsen, M., 2008. Diminished perception of light as a symptom of depression: further studies. J. Affect. Disord. 108, 235–240. https://doi.org/10.1016/j.jad.2007.10.021.

Frishman, L.J., 2018. Electrogenesis of the electroretinogram., in: Ryan's Retina. Chater 9. Elsevier, Edinburgh, New York.

Gagné, A.-.M., Lavoie, J., Lavoie, M.-.P., Sasseville, A., Charron, M.-.C., Hébert, M., 2010. Assessing the impact of non-dilating the eye on full-field electroretinogram and standard flash response. Doc. Ophthalmol. Adv. Ophthalmol. 121, 167–175. https://doi.org/10.1007/s10633-010-9242-1.

Gastinger, M.J., Tian, N., Horvath, T., Marshak, D.W., 2006. Retinopetal axons in mammals: emphasis on histamine and serotonin. Curr. Eye Res. 31, 655–667. https://doi.org/10.1080/02713680600776119.

Geoffroy, P.A., Schroder, C.M., Reynaud, E., Bourgin, P., 2019. Efficacy of light therapy versus antidepressant drugs, and of the combination versus monotherapy, in major depressive episodes: a systematic review and meta-analysis. Sleep Med Rev 48, 101213. https://doi.org/10.1016/j.smrv.2019.101213.

Gundogan, F.C., Erdurman, C., Durukan, A.H., Sobaci, G., Bayraktar, M.Z., 2007. Acute effects of cigarette smoking on multifocal electroretinogram. Clin. Experiment. Ophthalmol. 35, 32–37. https://doi.org/10.1111/j.1442-9071.2006.01384.x.

Hamilton, M., 1959. The assessment of anxiety states by rating. Br. J. Med. Psychol. 32, 50–55. https://doi.org/10.1111/j.2044-8341.1959.tb00467.x.

Hamon, M., Blier, P., 2013. Monoamine neurocircuitry in depression and strategies for new treatments. Prog. Neuropsychopharmacol. Biol. Psychiatry 45, 54–63. https://doi.org/10.1016/j.pnpbp.2013.04.009.

Hasin, D.S., Sarvet, A.L., Meyers, J.L., Saha, T.D., Ruan, W.J., Stohl, M., Grant, B.F., 2018. Epidemiology of Adult DSM-5 Major Depressive Disorder and Its Specifiers in the United States. JAMA Psychiatry 75, 336–346. https://doi.org/10.1001/jamapsychiatry.2017.4602.

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. Prog. Neuropsychopharmacol. Biol. Psychiatry 75, 10–15. https://doi.org/10.1016/j.pnpbp.2016.12.002.

Hirschfeld, R.M.A., Lewis, L., Vornik, L.A., 2003. Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. J. Clin. Psychiatry 64, 161–174.

Hoffmann, M.B., Bach, M., Kondo, M., Li, S., Walker, S., Holopigian, K., Viswanathan, S., Robson, A.G., 2021. ISCEV standard for clinical multifocal electroretinography (mfERG) (2021 update). Doc. Ophthalmol. Adv. Ophthalmol. 142, 5–16. https://doi.org/10.1007/s10633-020-09812-w.

Holder, G.E., Celesia, G.G., Miyake, Y., Tobimatsu, S., Weleber, R.G., 2010. International Federation of Clinical Neurophysiology: recommendations for visual system testing. Clin. Neurophysiol. 121, 1393–1409. https://doi.org/10.1016/j.clinph.2010.04.010.

Holma, M., Holma, I., Isometsä, E., 2020. Comorbid alcohol use disorder in psychiatric MDD patients: a five-year prospective study. J. Affect. Disord. 267, 283–288. https://doi.org/10.1016/j.jad.2020.02.024.

Hood, D.C., Bach, M., Brigell, M., Keating, D., Kondo, M., Lyons, J.S., Marmor, M.F., McCulloch, D.L., Palmowski-Wolfe, A.M., International Society For Clinical Electrophysiology of Vision, 2012. ISCEV standard for clinical multifocal electroretinography (mfERG) (2011 edition). Doc. Ophthalmol. Adv. Ophthalmol. 124, 1–13. https://doi.org/10.1007/s10633-011-9296-8.

Hoon, M., Okawa, H., Della Santina, L., Wong, R.O.L., 2014. Functional architecture of the retina: development and disease. Prog. Retin. Eye Res. 42, 44–84. https://doi.org/10.1016/j.preteyeres.2014.06.003.

Horton, J.C., Hoyt, W.F., 1991. The representation of the visual field in human striate cortex. A revision of the classic Holmes map. Arch. Ophthalmol. Chic. Ill 1960 109, 816–824. https://doi.org/10.1001/archopht.1991.01080060080030.

Hunt, G.E., Malhi, G.S., Lai, H.M.X., Cleary, M., 2020. Prevalence of comorbid substance use in major depressive disorder in community and clinical settings, 1990-2019: systematic review and meta-analysis. J. Affect. Disord. 266, 288–304. https://doi.org/10.1016/j.jad.2020.01.141.

Lavoie, J., Illiano, P., Sotnikova, T.D., Gainetdinov, R.R., Beaulieu, J.-.M., Hébert, M., 2014a. The electroretinogram as a biomarker of central dopamine and serotonin: potential relevance to psychiatric disorders. Biol. Psychiatry 75, 479–486. https://doi.org/10.1016/j.biopsych.2012.11.024.

Lavoie, J., Maziade, M., Hébert, M., 2014b. The brain through the retina: the flash electroretinogram as a tool to investigate psychiatric disorders. Prog. Neuropsychopharmacol. Biol. Psychiatry 48, 129–134. https://doi.org/10.1016/j.pnpbp.2013.09.020.

London, A., Benhar, I., Schwartz, M., 2013. The retina as a window to the brain-from eye research to CNS disorders. Nat. Rev. Neurol. 9, 44–53. https://doi.org/10.1038/nrneurol.2012.227.

Lucas, A., Thirion, A., Schwan, R., Krieg, J., Angioi-Duprez, K., Laprevote, V., Schwitzer, T., 2019. Association between increased retinal background noise and co-occurrent regular cannabis and alcohol use. Prog. Neuropsychopharmacol. Biol. Psychiatry 89, 335–340. https://doi.org/10.1016/j.pnpbp.2018.10.002.

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). Doc. Ophthalmol. Adv. Ophthalmol. 130, 1–12. https://doi.org/10.1007/s10633-014-9473-7.

Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry J. Ment. Sci. 134, 382–389.

Niciu, M.J., Ionescu, D.F., Richards, E.M., Zarate, C.A., 2014. Glutamate and its receptors in the pathophysiology and treatment of major depressive disorder. J. Neural Transm. Vienna Austria 1996 121, 907–924. https://doi.org/10.1007/s00702-013-1130-x.

Nivoli, A.M.A., Colom, F., Murru, A., Pacchiarotti, I., Castro-Loli, P., González-Pinto, A., Fountoulakis, K.N., Vieta, E., 2011. New treatment guidelines for acute bipolar depression: a systematic review. J. Affect. Disord. 129, 14–26. https://doi.org/10.1016/j.jad.2010.05.018.

Nogueira, R.M.T.B.L., Espínola, E.L., Lacerda, A.M., Santos, N.A., 2013. Mesopic Visual Contrast Sensitivity in Patients with Major Depression. Open J. Depress. 02, 82–86. https://doi.org/10.4236/ojd.2013.24014.

O'Rahilly, R., Müller, F., 1994. Neurulation in the normal human embryo. Ciba Found. Symp. 181, 70–82. https://doi.org/10.1002/9780470514559.ch5 discussion 82-89.

Pacek, L.R., Martins, S.S., Crum, R.M., 2013. The bidirectional relationships between alcohol, cannabis, co-occurring alcohol and cannabis use disorders with major depressive disorder: results from a national sample. J. Affect. Disord. 148, 188–195. https://doi.org/10.1016/j.jad.2012.11.059.

Perossini, M., Fornaro, P., 1990. Electroretinographic effects induced in humans by psychopharmacologic agents. Doc. Ophthalmol. Adv. Ophthalmol. 75, 1–6. https://doi.org/10.1007/BF00142587.

Robson, A.G., Nilsson, J., Li, S., Jalali, S., Fulton, A.B., Tormene, A.P., Holder, G.E., Brodie, S.E., 2018. ISCEV guide to visual electrodiagnostic procedures. Doc. Ophthalmol. Adv. Ophthalmol. 136, 1–26. https://doi.org/10.1007/s10633-017-9621-y.

Rock, P.L., Roiser, J.P., Riedel, W.J., Blackwell, A.D., 2014. Cognitive impairment in depression: a systematic review and meta-analysis. Psychol. Med. 44, 2029–2040. https://doi.org/10.1017/S0033291713002535.

Schwitzer, T., Henrion, M.-.L., Sarre, D., Albuisson, E., Angioi-Duprez, K., Giersch, A., Lalanne, L., Schwan, R., Laprevote, V., 2020. Spatial localization of retinal anomalies in regular cannabis users: the relevance of the multifocal electroretinogram. Schizophr. Res. 219, 56–61. https://doi.org/10.1016/j.schres.2019.01.013.

Schwitzer, T., Lavoie, J., Giersch, A., Schwan, R., Laprevote, V., 2015. The emerging field of retinal electrophysiological measurements in psychiatric research: a review of the findings and the perspectives in major depressive disorder. J. Psychiatr. Res. 70, 113–120. https://doi.org/10.1016/j.jpsychires.2015.09.003.

Schwitzer, T., Schwan, R., Albuisson, E., Giersch, A., Lalanne, L., Angioi-Duprez, K., Laprevote, V., 2017. Association Between Regular Cannabis Use and Ganglion Cell Dysfunction. JAMA Ophthalmol 135, 54–60. https://doi.org/10.1001/jamaophthalmol.2016.4761.

Schwitzer, T., Schwan, R., Angioi-Duprez, K., Giersch, A., Lalanne, L., Albuisson, E., Laprevote, V., 2018. Delayed bipolar and ganglion cells neuroretinal processing in regular cannabis users: the retina as a relevant site to investigate brain synaptic transmission dysfunctions. J. Psychiatr. Res. 103, 75–82. https://doi.org/10.1016/j.jpsychires.2018.04.021.

Schwitzer, T., Schwan, R., Angioi-Duprez, K., Lalanne, L., Giersch, A., Laprevote, V., 2019. Cannabis use and human retina: the path for the study of brain synaptic

transmission dysfunctions in cannabis users. Neurosci. Biobehav. Rev. 106, 11–22. https://doi.org/10.1016/j.neubiorev.2018.12.001.
Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59 (Suppl 20), 22–33 quiz 34-57.
Silverstein, S.M., Rosen, R., 2015. Schizophrenia and the eye. Schizophr. Res. Cogn. 2, 46–55. https://doi.org/10.1016/j.scog.2015.03.004.
Solomon, D.A., Leon, A.C., Maser, J.D., Truman, C.J., Coryell, W., Endicott, J., Teres, J.J., Keller, M.B., 2006. Distinguishing bipolar major depression from unipolar major depression with the screening assessment of depression-polarity (SAD-P). J. Clin. Psychiatry 67, 434–442. https://doi.org/10.4088/jcp.v67n0315.
Stewart, E.E.M., Valsecchi, M., Schütz, A.C., 2020. A review of interactions between peripheral and foveal vision. J. Vis. 20 https://doi.org/10.1167/jov.20.12.2.
Varghese, S.B., Reid, J.C., Hartmann, E.E., Keyser, K.T., 2011. The effects of nicotine on the human electroretinogram. Invest. Ophthalmol. Vis. Sci. 52, 9445–9451. https://doi.org/10.1167/iovs.11-7874.
Wesner, M.F., Tan, J., 2006. Contrast sensitivity in seasonal and nonseasonal depression. J. Affect. Disord. 95, 19–28. https://doi.org/10.1016/j.jad.2006.03.028.
Wiechmann, A.F., Sherry, D.M., 2013. Role of melatonin and its receptors in the vertebrate retina. Int. Rev. Cell Mol. Biol. 300, 211–242. https://doi.org/10.1016/B978-0-12-405210-9.00006-0.
Witkovsky, P., 2004. Dopamine and retinal function. Doc. Ophthalmol. Adv. Ophthalmol. 108, 17–40.
Wu, S.M., Maple, B.R., 1998. Amino acid neurotransmitters in the retina: a functional overview. Vision Res 38, 1371–1384.