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Retinal electroretinogram features can detect depression state and treatment response in adults: a machine learning approach

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Highlights:

- **Retinal function is relevant to study brain function in major depressive disorder**
- **Retinal dysfunctions were observed with electroretinogram in major depressive disorder**
- **Signal processing and machine learning tools were applied on electroretinogram data**
- **Signal processing and machine learning tools can help clinical decision**

ABSTRACT

Background: Major depressive disorder (MDD) is a major public health problem. The retina is a relevant site to indirectly study brain functioning. Alterations in retinal processing were demonstrated in MDD with the pattern electroretinogram (PERG). Here, the relevance of signal processing and machine learning tools applied on PERG was studied.

Methods: PERG – whose stimulation is reversible checkerboards – was performed according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standards in 24 MDD patients and 29 controls at the inclusion. PERG was recorded every 4 weeks for 3 months in patients. Amplitude and implicit time of P50 and N95 were evaluated. Then, time/frequency features were extracted from the PERG time series based on wavelet analysis. A statistical model has been learned in this feature space and a metric aiming at quantifying the state of the MDD patient has been derived, based on minimum covariance determinant (MCD) mahalanobis distance.

Results: MDD patients showed significant increase in P50 and N95 implicit time ($p=0,006$ and $p=0,0004$, respectively, Mann–Whitney U test) at the inclusion. The proposed metric extracted from the raw PERG provided discrimination between patients and controls at the inclusion ($p=0,0001$). At the end of the follow-up at week 12, the difference between the metrics extracted on controls and patients was not significant ($p=0,07$), reflecting the efficacy of the treatment.

Conclusions: Signal processing and machine learning tools applied on PERG could help clinical decision in the diagnosis and the follow-up of MDD in measuring treatment response.

Keywords: major depressive disorder, retina, electroretinogram, wavelet analysis, machine learning, help for clinical decision

1. Introduction

Major depressive disorder (MDD) is a common public health issue, which concerns 300 million people worldwide and has rapid kinetics (Smith, 2014). It is the leading cause of disability worldwide, with a notable impact on life quality, a higher risk of mortality and one of the main risk factors for suicide. Up to 30% of MDD patients do not respond to their antidepressant treatments and 50-60% do not achieve adequate response (Fava, 2003; Smith, 2014).

MDD diagnosis and treatment are very challenging. There is no current objective tool to help practitioners in diagnosis as well as in evaluating and predicting the response to treatments in order to adjust individualized and personalized therapeutics for the patient. The diagnosis of MDD is currently made by medical interview. During this interview, the clinician can be helped by subjective scales such as the Hamilton Rating Scale for Depression (HRSD; HAM-D) but these tools are dependent on the patient's contribution (Bagby et al., 2004). There are no valid and reliable tools that can help medical practitioners in MDD in the choice of antidepressant and its effective dose. For precision psychiatry, there is an urgent need to improve diagnosis in the case of differential diagnosis, in detecting subgroups of patients or specific symptoms such as suicidal ideation in order to predict the better therapeutics for the patients.

One of the current challenges in neuropsychiatric research is to develop new investigative approaches, aided by the processing and analysis such as machine learning, to find tools that are reliable, objective, reproducible and easy to implement, and independent of the therapist and the patient. In this context, electrophysiological techniques are relevant and promising measurements (Cosker et al., 2020; Lavoie et al., 2014b; London et al., 2013; Schwitzer et al., 2015, 2017b). To the best of our knowledge, only one study has applied

machine learning to electroencephalograms (EEG) in MDD (Rajpurkar et al., 2020). In this study, a machine learning algorithm based on a decision tree was applied to the EEG data coupled with pre-treatment symptom scores to separate the populations of MDD according to their pharmacological treatments. Machine learning and discriminant analysis of EEGs proved to be useful in predicting the efficacy of antidepressants based on the main symptoms of depression and the characteristics of the pre-treatment EEG.

The retina is considered as a crucial and relevant site to indirectly investigate brain function in neuropsychiatric disorders (Bubl et al., 2010a; Lavoie et al., 2014a; London et al., 2013; Schwitzer et al., 2017b). The retina is an anatomical and developmental extension of the central nervous system (CNS), which consists of a complex neural network constituted by specific neurons and interconnected by synapses (Hoon et al., 2014). Retinal neurons share similar anatomical and functional properties to brain neurons (Hoon et al., 2014). They emit electrical signals in the form of membrane potentials and action potentials, such as brain neurons. They are endowed with several complex neurotransmission signalling pathways, including the same pathways that are detected in the brain and involved in the pathophysiology of MDD – serotonin, dopamine, and glutamate, to name a few (Hoon et al., 2014). Retinal function is altered in many neuropsychiatric disorders involving different pathophysiological mechanisms such as neurotransmission abnormalities, inflammation, and neurodegeneration, suggesting that brain abnormalities observed in these disorders may be detected at the level of the retina (Lavoie et al., 2014b, 2014a; London et al., 2013; Schwitzer et al., 2015). For example, retinal processing is impaired in depression, schizophrenia, Parkinson disease, Alzheimer disease, and substance use disorders, to name a few (Bernardin et al., 2017; Cosker et al., 2021, 2020; London et al., 2013; Lucas et al., 2018; Schwitzer et al., 2021, 2019, 2016; Youssef et al., 2019). Retinal function is easy to access and retinal

electrophysiological tests are relatively easy to achieve, rapid, inexpensive, and non-invasive (Bach et al., 2013).

Among all retinal neuronal stages, the ganglion cell layer is considered as the most relevant for studying brain functioning indirectly (Schwitzer et al., 2017b). The retinal ganglion stage is the final and most integrated retinal stage and acts as an anatomical and functional relay between the retina and the brain through the nerve optic formed by the axons of the ganglion cells. These cells are composed of cell body, axons, and dendrites and provide response in the form of action potentials, such as brain neurons. Ganglion cells' functioning is altered in many neurologic, psychiatric and neurodegenerative disorders. Retinal ganglion cells' electrical activity response is recorded with the pattern electroretinogram (PERG), which is an electrophysiological technique (Bach et al., 2013). PERG measurements use checkerboard stimuli such as visual evoked potentials (VEP) to record an electrical signal originating from central neurons. PERG measures have already allowed the differentiation of MDD patients and healthy subjects, the response to treatment to be followed, and a correlation with VEP, suggesting that visual retinal ganglion cells and cortical function are correlated (Bubl et al., 2015, 2012, 2010b). Schematic representation of the retina and of a PERG typical trace is presented Figure 1.

The assumption posed for this study was therefore that the extraction of PERG indicators could be an indirect measure reflecting a set of functional and behavioural alterations in the underlying neuronal cell biology. The objectives of this study were to evaluate amplitude and implicit time of P50 and N95 of the PERG in MDD patients and controls and to determine whether PERG holds relevant information in the diagnosis and

evaluation of treatment response in MDD using signal processing and machine learning techniques.

2. Methods and Materials

2.1. Population and ethics statement

Patients with MDD (n=24) were recruited from among psychiatric patients, hospitalized or not, with regular follow-up with a psychiatrist, via documentation or recommendation by their doctor. The data were collected from 16 January 2019 to 31 December 2019. The matching healthy controls (n=29) were recruited from two other cohorts: the CAUSA MAP study (NCT02864680), who were recruited among the general population via a special press campaign from 11 February 2014 to 30 June 2016; and the ERICA study (NCT0381897), who were recruited among the general population via a special press campaign from 01 March 2019 to 30 April 2021. Prior to taking part in this study, MDD patients provided their detailed medical history and treatments (current and past), underwent a full psychiatric evaluation (Mini-International Neuropsychiatric Interview – MINI, Montgomery Asberg Depression Rating Scale – MADRS, Epworth Sleepiness Scale – ESS, HAMILTON-A, Pittsburg Sleep Quality Index – PSQI) and a cognitive evaluation, and signed consent forms detailing all aspects of the research. MDD participants received compensation in the form of €15 in gift vouchers, at the end of the study. The study protocol met the requirements of the Helsinki Declaration and was approved by the Ethics Committee of Nancy University Hospital. This preliminary study is part of a bigger project, LUMIDEP, which is evaluating complete retinal function and structure in MDD patients receiving active luminotherapy and treatment as usual or placebo luminotherapy and treatment as usual.

2.2. Inclusion criteria, clinical and biological assessments

The main inclusion criterion for the depressive group was having a diagnosis of Major Depressive Disorder according to the DSM-IV criteria, assessed by the Mini-International Neuropsychiatric Interview (MINI) test. Other inclusion criteria were having received complete information about the clinical trial and signed a written informed consent. All participants were aged 18 to 60 years old, had no psychiatric disorder from the DSM-IV axes I, apart from depressive and anxiety disorder; no seasonal disorder; no previous or current bright light therapy treatment; no lack of follow-up with a psychiatrist; and no suicide risk. They should not have a retinal or neurological disease, be participating in another study (including exclusion period), have a disability, be pregnant or breastfeeding, be deprived of liberty by a judicial or administrative decision, be subject to psychiatric care under duress, be admitted to a health or social institution for purposes other than research, be an adult subject to a legal protection measure (guardianship, curatorship, safeguarding justice), or be unable to express consent. All subjects were covered by social security.

The inclusion criteria for healthy control subjects were the same as those of the CAUSA MAP study, as described in previous studies (Dartois et al., 2021; Polli et al., 2020; Schwitzer et al., 2020, 2018, 2017a) and the ERICA study (NCT0381897).

All fared normally in an ophthalmic evaluation, which included visual acuity and a fundoscopic examination. Importantly, visual acuity measured with the Monoyer scale was at least 10/10 in each eye for all participants. None of the participants reported visual symptoms. If participants reported alcohol dependence based on their score in the Alcohol Use Disorders Identification Test (AUDIT) they were excluded from the study. The Mini-International

Neuropsychiatric Interview (MINI) was used to assess current and past history of psychiatric diseases and substance use.

2.3. Experimental protocol

PERG was performed according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standards (Bach et al., 2013). We used the MonPackONE system (Metrovision, Pérenchies, France) for the stimulation and the recording. We collected electrical signals from both eyes, simultaneously. Averaged retinal responses were obtained from each eye. Electrical signals were collected on non-dilated pupils, with DTL (Dawson Trick Litzkow) electrodes placed at the bottom of the conjunctival sac. Ground and reference electrodes were fixed to the forehead and external canthi. A black and white contrast reversible checkerboard, with 0.8° check size, 93.3% contrast level, 100 candela/m² constant luminance white area, and 4 reversals per second was used. The participants were positioned one metre from the screen. In the case of participants with refractive disorders, an appropriate optic correction was provided. At least 220 responses were recorded for each participant, with constant ambient room lighting to achieve the best signal-to-noise ratio. PERG was performed at the inclusion (n=24), week 4 (n=16), week 8 (n=13) and week 12 (n=14) with the same protocol. Mean responses of left and right eyes are averaged, the analyzed signals contained 240 samples between -16ms to 195.6ms around the instant of the visual stimuli (sampling rate 1024Hz). At each visit, patients completed MADRS, MADRS-self and HAMILTON scale.

2.4. Analysis

The PERG data were analyzed using an ophthalmic monitor (Metrovision, Pérenchies, France). Two main components are usually described on a typical PERG trace: an electropositive component, P50, followed by an electronegative component, N95. N95 is believed to reflect the response of retinal cells. P50 reflects the response of the retinal ganglion cells and macular photoreceptors, and is used to evaluate macular function. Two main parameters are derived from P50 and N95, referred to as the amplitude, measured in microvolts (μV), and the implicit time, measured in milliseconds (ms). N95 amplitude is measured from the trough of N95 to the peak of P50. P50 amplitude is measured from the trough of the inconstant N35—or from the baseline—to the peak of P50. Implicit time denotes the time taken to reach the maximum N95 and P50 amplitudes. Besides the analysis of these well known characteristics, we considered a more global analysis of the signal based on wavelet decomposition, which consists in a time/frequency analysis of the signal summing up the main characteristics of the signal dynamics to a few number of coefficients. A feature selection has been applied on these coefficients to retain only those with the highest discrimination power, defined here as these having a distribution differing the most from a normal distribution (Lilliefors test). Finally, by means of Principal Component Analysis (PCA), we reduced this coefficient space to preserve the components holding most of the energy (i.e. most of the information). Two components were preserved, and a distance to normality was defined in this two-dimensional space as a Mahalanobis distance based on minimum covariance determinant (MCD-Mahalanobis) estimated on the control data. For each PERG acquisition this distance was computed (after left/right eyes averaging). More details on these different methodological steps are given in supplementary material.

2.5. Statistical Analysis

Depending on the non-parametric distribution of the quantitative variables included in the analyses, a Mann–Whitney U test and Chi-square test were used when appropriate. An alpha risk of 0.05% was used. Statistical analyses were performed using IBM SPSS Statistics 22.0 (IBM corp.). More details on the analysis of the signal based on wavelet decomposition are given in supplementary material.

3. Results

The demographic, substance use, clinical and PERG data of the participants at the inclusion and during the follow-up are described in Table 1. At the inclusion, differences were noted between the controls and MDD patients in terms of gender ($p < 0.05$), age ($p < 0.05$) and years of education ($p < 0.05$), but no relevant differences were observed between the groups in terms of alcohol use ($p = 0.78$ for average alcohol consumption/week, $p = 0.46$ for AUDIT score). MDD patients showed significant increase in P50 and N95 implicit time ($p = 0.006$ and $p = 0.0004$, respectively; Mann–Whitney U test). Scores at the MADRS hetero assessment, MADRS self-assessment and Hamilton Depression scales were significantly decreased between week 12 and the inclusion ($p = 0.0002$; 0.0005 and 0.00001 respectively, Mann–Whitney U test).

Our model and the derived MCD-Mahalanobis distance are based on a hypothesis of multivariate normality for the control data projected in the selected feature space. The validity of this hypothesis has been evaluated using Mardia's multivariate normality test, considering skewness (corrected for small data, $p = 0.16$) as well as kurtosis ($p = 0.84$) of the control data distribution. Hence, the H_0 normal hypothesis could not be rejected at 0.05 risk level for both statistics, confirming the validity of the proposed model.

The proposed MCD-Mahalanobis distance was also able to discriminate between controls and patients at inclusion ($p = 0.0002$) (Figure 2). This distance at week 4 and 8 tends to reduce as the treatment progresses but remains significantly different from controls

($p=0,0029$ and $p=0,0021$ respectively) (Figure 2). At week 12, no significant difference was found at this stage of the treatment when compared with the controls ($p=0.23$) (Figure 2). We compared this distance extracted from the PERG data with the MADRS/MADRSself data collected at inclusion and at week 4, 8 and 12. There is at the inclusion of participants significantly higher scores than for week 4 ($p=0,0078$ for MADRS and $p=0,0197$ for MADRSself), followed by a sharp decline to mild to non-existent depression scores in week 8 and 12 (scores all below 15 and 10 respectively, $p=0,0002$ and $p=0,0001$ for MADRS between inclusion and week 8 and 12 respectively; $p=0,0014$ and $p=0,0005$ for MADRSself)(Figure 3).

4. Discussion

Here, we observed that: 1- MDD patients showed an increase in P50 and N95 implicit time of the PERG at the inclusion. 2- PERG can help to distinguish a healthy population from a population of MDD subjects, with the help of a machine learning algorithm and MCD-Mahalanobis distance. 3- PERG can also be used to assess the course of MDD during treatment. Indeed, the MCD-Mahalanobis distance tends to reduce as the treatment progresses and normalizes with remission. In MDD patients who were treated for 12 weeks and who have observed a regression of depressive symptoms objectified by MADRS, MCD-Mahalanobis distance was reduced and there was no significant difference at week 12 between patients and controls. 4- Clinical features of MDD evaluated by the MADRS scale and retinal electrophysiological properties evaluated by PERG analyzed by an artificial intelligence algorithm share a similar evolution, suggesting that subjective and objective measures are linked.

The fact that PERG analyzed by machine learning techniques can help to distinguish a healthy population from a population with MDD is very promising since the diagnosis constitutes a real prospect in MDD. Making a diagnosis of MDD is relatively easy. However, the differential diagnosis -with bipolar depression for example- as well as the identification of sub-groups of MDD remain critical perspectives. Our findings open the way for these issues to be resolved. In young people, some psychiatric diseases can share similar symptoms with MDD but do not share similar treatment, leading to inadequate care for the patient. In young people without medical history, it is really complicated to affirm with an absolute certainty whether the first depressive episode is linked to MDD or to bipolar disorder. Previous studies support our findings and have already highlighted the usefulness of retinal electrophysiology

in the differential diagnosis of mental disorders (Hébert et al., 2020). In this study, the authors showed similarities and significant differences between flash ERG (fERG) recordings of 150 patients with schizophrenia and 151 patients with bipolar disorder. In both disorders, they observed reduced cone a-wave amplitude, prolonged b-wave latency, and reduced mixed rod-cone a- and b-wave amplitudes. Interestingly, reduced cone b-wave amplitude was detected only in subjects with schizophrenia. Taken together, these findings support that mental disorders have specific retinal characteristics. In this context, the help of machine learning could strengthen the accuracy and reliability of these findings. Another critical perspective in caring for patients is the early detection of at-risk subjects. MDD, once installed, has a very negative impact on the quality of life of patients, supporting early detection, objective and intervention in high-risk subjects. A previous study performed a detailed analysis of the interaction between depressive symptom severity, functioning, and quality of life (QOL) in 319 patients with MDD using the Quality of Life - Enjoyment, and Satisfaction Questionnaire (Q-LES-Q) (Ishak et al., 2013). The authors showed that the quality of life is significantly impaired in MDD, with a mean Q-LES-Q score for this study population of 39.8% (SD = 16.9), whereas the community norm average is 78.3%. Interestingly, previous studies have already evoked the usefulness of ERG in detecting patients at risk of developing mental illnesses. As an example, Hébert et al. (2010) studied, several years before the first symptoms of the disease appeared, fERG in 29 medication-free subjects, descendants of multigenerational families affected by schizophrenia or bipolar disorder (Hébert et al., 2010). In these subjects, they observed a diminution of rod b-wave Vmax amplitude, a trend for lower cone a-wave amplitude, and a trend for a longer rod b-wave implicit time at Vmax. fERG rod and cone abnormal responses in adult patients having schizophrenia, bipolar disorder or MDD have also been reported. We suppose that some ERG anomalies observed in subjects with schizophrenia or bipolar disorder would emerge in at risk young subjects and

that ERG abnormalities have a neurodevelopmental origin. Gagné et al. compared the fERG of 99 offspring of patients having schizophrenia, bipolar disorder or MDD and the fERG of 223 healthy controls balanced for sex and age (Gagné et al., 2020). Compared to the healthy controls, the fERG of offspring were characterized by an increase in cone b-wave latency, a decrease in rod b-wave amplitude, and an increase in rod b-wave latency. As previously described, fERG rod and cone responses of adult patients having schizophrenia, bipolar disorder or MDD share similar characteristics and could be detectable in genetically high-risk offspring (Gagné et al., 2015; Hébert et al., 2020). These results give the possibility of using ERG to detect early electrophysiological features in subjects at risk of developing a mental disorder. Future studies will apply artificial intelligence algorithms on ERG measures, with the help of machine learning, to enhance the powerfulness of retinal measurements in detecting populations of patients at risk of developing mental disorders.

In MDD, medical practitioners are confronted with partial or no response to pharmacotherapy. One goal is to find the most adapted and personalized pharmacological treatment according to characteristics – kind of symptoms, suspected neurotransmitter deficits, etc. – of each patient. In MDD, pharmacotherapy is a long treatment that takes several weeks to be effective, and needs to be regularly adjusted depending on the patient's response and according to the stage of the disease. Currently, it is adjusted to the symptoms alleged by the patients and those found by therapists. As a result, therapeutic adjustments remain highly subjective. The risk is to give a reduced dosage of treatment, reducing the chances of efficacy. Contrarily, giving high-dose treatment as well as treating for too long while the depressive state is resolved, increases the risk of side effects. In this context, the retinal function has given interesting indicators. Hébert et al. recorded fERG in 100 patients with MDD – of whom 17 were drug-free – and 100 healthy controls (Hébert et al., 2017). A sizable decrease in the cone a- and b- wave amplitudes at Vmax was observed in drug-free

patients, which was not present in medicated patients. These results suggest a possible normalization of ERG parameters in medicated patients. These are promising findings in favour of the relevance of ERG in the follow-up of pharmacological treatment and in the evaluation of their efficacy. This is supported by the fact that the retina is endowed with complex neurotransmission signalling pathways –serotonergic, dopaminergic, among others – targeted by antidepressants in the CNS. Here, we showed similar results suggesting that PERG measures analyzed with the help of machine learning algorithms can separate MDD subjects in the course of treatment from healthy subjects or depressive subjects in early illness.

This study has limitations and implied several perspectives. Our results are extracted from a preliminary analysis with a low number of subjects. Further investigations with a high number of subjects and with sub-groups of MDD patients are required to achieve consolidated statistics and conclude on the relevance of this technique to both helping diagnosis and the evaluation of treatment response in MDD. The use of tobacco in MDD patients does not affect the N95 implicit time (Dartois et al., 2021). The differences in gender and age between groups are not sufficient to explain alterations in P50 and N95 observed in patients since gender seems to be not involved in PERG modulations and the between groups difference in age is relatively low to explain the results presented here (Celesia et al., 1987; Coríci et al., 2015; Porciatti et al., 1992). These measures and signal analysis should be replicated in other neuropsychiatric pathological conditions –bipolar disorders, schizophrenia, neurodegenerative disorders, autism spectrum disorder – to refine the sensitivity and the specificity of these measures in the diagnosis of main neuropsychiatric disorders. This technique also should be able to help clinicians in the differential diagnosis of specific pathological conditions such as the differential diagnosis between unipolar and bipolar depression. Here, patients received different types of treatments and we evaluated the efficacy of the global treatment and not the

efficacy of the isolated treatment. Various sub-groups of patients, with specific and isolated treatment, would be required in future studies to evaluate the relevance of this technique in the evaluation of the response of each treatment. In routine clinical evaluation, these measures should also be able to detect patients who will develop treatment resistance, in order to adjust pharmacotherapy at an early stage. This technique should in the future be able to detect and separate responder and no-responder patients. Finally, in order to be used in clinical practice, these measures should be easy to use, mobile, automatized with remote analysis and usable in ambulatory centres and in centres which are situated in remote areas, and not only usable in specific care centres.

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Author contributions :

All the authors contributed to write the manuscript, concurred with the submission and have approved the final manuscript.

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.
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Declaration of competing interests: the authors report no biomedical financial interests or potential conflicts of interest.

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5. References

- 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* 126, 1–7. <https://doi.org/10.1007/s10633-012-9353-y>
- Bagby, R.M., Ryder, A.G., Schuller, D.R., Marshall, M.B., 2004. The Hamilton Depression Rating Scale: has the gold standard become a lead weight? *Am J Psychiatry* 161, 2163–2177. <https://doi.org/10.1176/appi.ajp.161.12.2163>
- Bernardin, F., Schwan, R., Lalanne, L., Ligier, F., Angioi-Duprez, K., Schwitzer, T., Laprevote, V., 2017. The role of the retina in visual hallucinations: A review of the literature and implications for psychosis. *Neuropsychologia* 99, 128–138. <https://doi.org/10.1016/j.neuropsychologia.2017.03.002>
- 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* 201, 151–158. <https://doi.org/10.1192/bjp.bp.111.100560>
- Bubl, E., Kern, E., Ebert, D., Bach, M., Tebartz van Elst, L., 2010a. 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., Bach, M., Tebartz van Elst, L., 2010b. Seeing Gray When Feeling Blue? Depression Can Be Measured in the Eye of the Diseased. *Biological 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>
- Celesia, G.G., Kaufman, D., Cone, S., 1987. Effects of age and sex on pattern electroretinograms and visual evoked potentials. *Electroencephalogr Clin Neurophysiol* 68, 161–171. [https://doi.org/10.1016/0168-5597\(87\)90023-2](https://doi.org/10.1016/0168-5597(87)90023-2)
- Corîci, A.C., Alexandru, D.O., Corîci, O.M., Puianu, M., Iancău, M., Ștefănescu-Dima, A., 2015. Variability of Normal Values of Electroretinogram Parameters Due to Aging in Healthy Individuals. *Curr Health Sci J* 41, 29–34. <https://doi.org/10.12865/CHSJ.41.01.04>
- Cosker, E., Moulard, M., Baumann, C., Luc, A., Angioi-Duprez, K., Laprêvotte, V., Schwan, R., Schwitzer, T., 2021. Complete evaluation of retinal function in Major Depressive Disorder: From central slowdown to hyperactive periphery. *J Affect Disord* 295, 453–462. <https://doi.org/10.1016/j.jad.2021.08.054>
- Cosker, E., Schwan, R., Angioi-Duprez, K., Laprêvotte, 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>
- Dartois, M., Haudiquet, N., Albuissou, E., Angioi-Duprez, K., Schwan, R., Laprêvotte, V., Schwitzer, T., 2021. Retinal dysfunctions in regular tobacco users: The retina as a window to the reward circuit in addictive disorders. *J Psychiatr Res* 136, 351–357. <https://doi.org/10.1016/j.jpsychires.2021.02.023>
- Fava, M., 2003. Diagnosis and definition of treatment-resistant depression. *Biol. Psychiatry* 53, 649–659.
- Gagné, A.-M., Hébert, M., Maziade, M., 2015. Revisiting visual dysfunctions in schizophrenia from the retina to the cortical cells: A manifestation of defective neurodevelopment. *Prog Neuropsychopharmacol Biol Psychiatry* 62, 29–34. <https://doi.org/10.1016/j.pnpbp.2015.04.007>
- Gagné, A.-M., Moreau, I., St-Amour, I., Marquet, P., Maziade, M., 2020. Retinal function anomalies in young offspring at genetic risk of schizophrenia and mood disorder: The

meaning for the illness pathophysiology. *Schizophr Res* 219, 19–24.
<https://doi.org/10.1016/j.schres.2019.06.021>

Hébert, M., Gagné, A.-M., Paradis, M.-E., Jomphe, V., Roy, M.-A., Mérette, C., Maziade, M., 2010. Retinal Response to Light in Young Nonaffected Offspring at High Genetic Risk of Neuropsychiatric Brain Disorders. *Biological Psychiatry* 67, 270–274.
<https://doi.org/10.1016/j.biopsych.2009.08.016>

Hébert, M., Mérette, C., Gagné, A.-M., Paccalet, T., Moreau, I., Lavoie, J., Maziade, M., 2020. The Electroretinogram May Differentiate Schizophrenia From Bipolar Disorder. *Biol Psychiatry* 87, 263–270. <https://doi.org/10.1016/j.biopsych.2019.06.014>

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>

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

Ishak, W.W., Balayan, K., Bresee, C., Greenberg, J.M., Fakhry, H., Christensen, S., Rapaport, M.H., 2013. A descriptive analysis of quality of life using patient-reported measures in major depressive disorder in a naturalistic outpatient setting. *Qual Life Res* 22, 585–596.
<https://doi.org/10.1007/s11136-012-0187-6>

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., 2018. 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>

Polli, L., Schwan, R., Albuissou, E., Malbos, L., Angioi-Duprez, K., Laprevote, V., Schwitzer, T., 2020. Oscillatory potentials abnormalities in regular cannabis users: Amacrine cells dysfunction as a marker of central dopaminergic modulation. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 110083.
<https://doi.org/10.1016/j.pnpbp.2020.110083>

Porciatti, V., Burr, D.C., Morrone, M.C., Fiorentini, A., 1992. The effects of aging on the pattern electroretinogram and visual evoked potential in humans. *Vision Res* 32, 1199–1209.
[https://doi.org/10.1016/0042-6989\(92\)90214-4](https://doi.org/10.1016/0042-6989(92)90214-4)

Rajpurkar, P., Yang, J., Dass, N., Vale, V., Keller, A.S., Irvin, J., Taylor, Z., Basu, S., Ng, A., Williams, L.M., 2020. Evaluation of a Machine Learning Model Based on Pretreatment Symptoms and Electroencephalographic Features to Predict Outcomes of Antidepressant Treatment in Adults With Depression: A Prespecified Secondary Analysis of a Randomized Clinical Trial. *JAMA Netw Open* 3, e206653.
<https://doi.org/10.1001/jamanetworkopen.2020.6653>

Schwitzer, T., Henrion, M.-L., Sarre, D., Albuissou, 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., Robert, M.P., Giersch, A., Angioi-Duprez, K., Ingster-Moati, I., Pon-Monnier, A., Schwan, R., Laprevote, V., 2016. Transient Retinal Dysfunctions after Acute Cannabis Use. *Eur Addict Res* 22, 287–291. <https://doi.org/10.1159/000446823>

Schwitzer, T., Schwan, R., Albuisson, E., Bugin, C., Zech, G., Angioi-Duprez, K., Bernardin, F., Laprévoté, V., 2021. Delayed on- and off-retinal responses of cones pathways in regular cannabis users: An On-Off flash electroretinogram case-control study. *J Psychiatr Res* 136, 312–318. <https://doi.org/10.1016/j.jpsychires.2021.02.033>

Schwitzer, T., Schwan, R., Albuisson, E., Giersch, A., Lalanne, L., Angioi-Duprez, K., Laprevote, V., 2017a. 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>

Schwitzer, T., Schwan, R., Bubl, E., Lalanne, L., Angioi-Duprez, K., Laprevote, V., 2017b. Looking into the brain through the retinal ganglion cells in psychiatric disorders: A review of evidences. *Prog. Neuropsychopharmacol. Biol. Psychiatry*. <https://doi.org/10.1016/j.pnpbp.2017.03.008>

Smith, K., 2014. Mental health: a world of depression. *Nature* 515, 181. <https://doi.org/10.1038/515180a>

Youssef, P., Nath, S., Chaimowitz, G.A., Prat, S.S., 2019. Electroretinography in psychiatry: A systematic literature review. *Eur Psychiatry* 62, 97–106. <https://doi.org/10.1016/j.eurpsy.2019.09.006>

Table:

***Table 1:** Demographic, substance use, clinical and pattern electroretinogram data of the participants at the inclusion and during the follow-up of the patients*

Figures:

Figure 1: Schematic representation of the retina and of a pattern electroretinogram's (PERG) typical trace with two main components named P50 and N95 waves

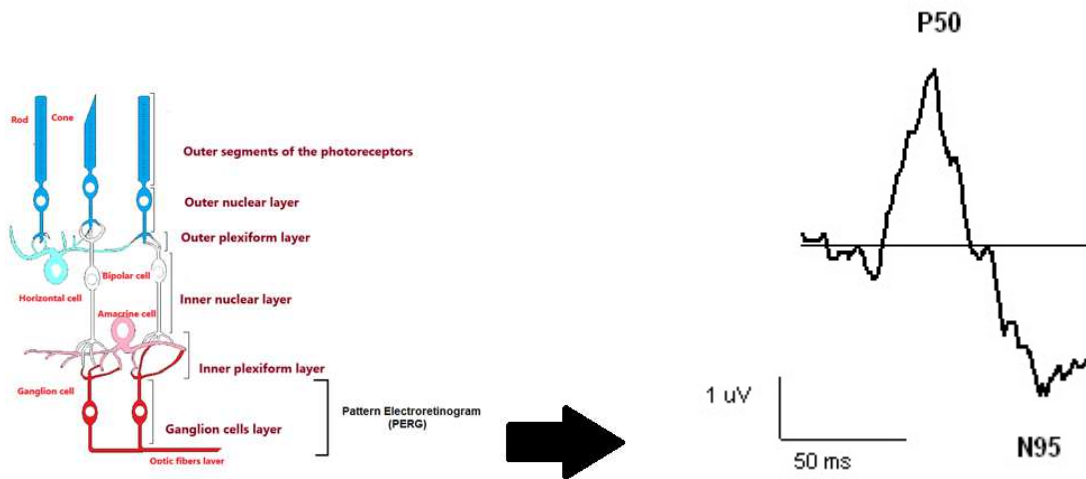


Figure 2: Tracking of the MCD-Mahalanobis distance along the 4 stages of the treatment. Little change in distributions up to week 8, a sharper (albeit not statistically significant, $p > 0,05$) decrease in week 12. The differences between healthy controls and patients at inclusions, week 4 and week 8 respectively are significant ($p < 0.01$), but not those between healthy controls and week 12, $p > 0,05$).

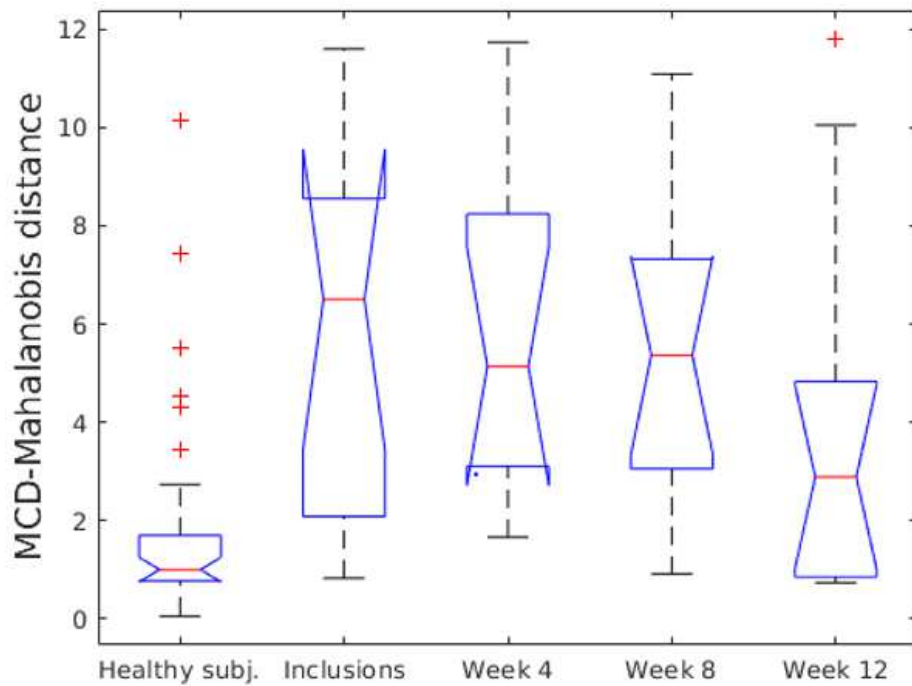
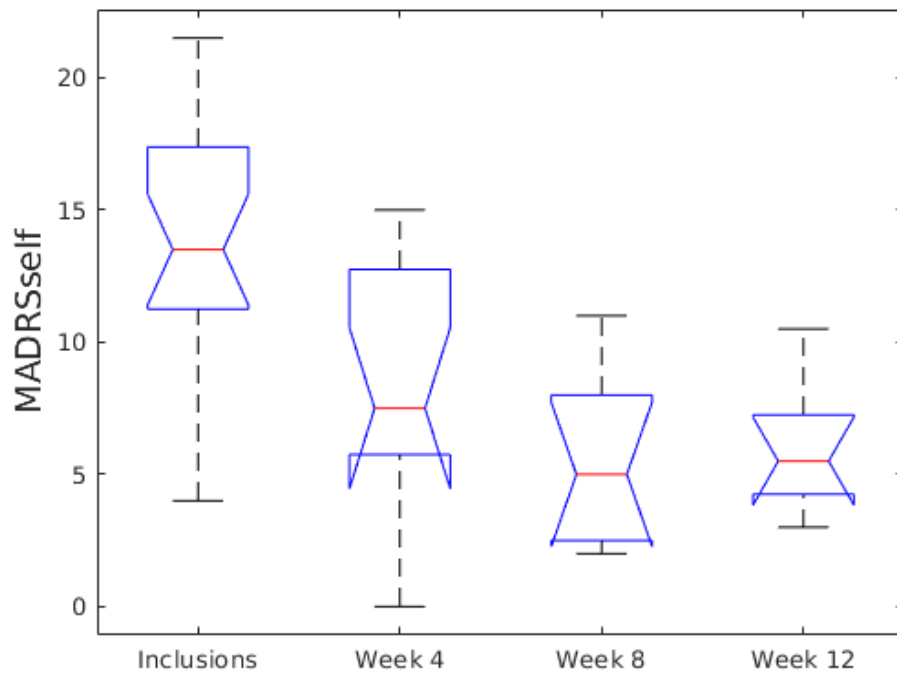


Figure 3: Inclusion with significantly higher scores of MADRSself than for the next steps ($p < 0,05$), then a sharp decline to mild to non-existent depression scores in week 8 and 12 (scores all below 15 and 10 respectively), with a transition in week 4.



	Gender (male/female) a,d	Age (years) b,c	Education (years) b,c	Average number of alcohol uses/week b,c	Alcohol Use Disorders Identification Test (AUDIT) scores b,c	Fagerströ m Test scores b	Average number of cigarette s/day b	Average number pack- years of cigarettes b	P50 Implicit Time (ms) b,c (n=21 for MDD)	P50 Amplitude (µV) b,c (n=21 for MDD)	N95 Implicit Time (ms) b,c (n=21 for MDD)	N95 amplitude (µV) b,c (n=21 for MDD)
Patients with major depressive disorder (n= 24)	6 / 18	41,5 (32 - 49)	13 (11,5 - 14)	1(0 – 4,5)	3,5 (1 – 7,5)	0,5 (0 - 5)	3,5 (0 -15)	3,7 (0 – 17)	51,75 (50,85:53,95)	2,25 (1,80:2,70)	95,10(91,60:99,20)	-3,20(-3,80:-2,40)
Controls (n=29)	21 / 8	25 (23 – 27)	15 (14 - 16)	1 (0 – 3)	3 (1 – 4)	-	-	-	48,65 (47,30:50,40)	2,35 (2,15:2,65)	88,95 (84,50:91,10)	-3,75 (-4,60:-3,15)
P-value	<i>p</i> <0,05	<i>p</i> <0,05	<i>p</i> <0,05	<i>p</i> =0,78	<i>p</i> =0,46	-	-	-	<i>p</i> =0,006	<i>p</i> =0,640	<i>p</i> = 0,0004	<i>p</i> =0,131

Categorical variable represented as frequencies ^a

Quantitative variable represented as median and interquartile range ^b

Mann-Whitney U test ^c

Chi-Square test ^d

MDD Group	Montgomery- Asberg Depression Rating Scale (MADRS) Hetero assessment Score	Montgomery- Åsberg Depression Rating Scale (MADRS) self assessment Score	Hamilton Depression Scale Score	Implicit Time (µV)	Amplitude (µV)	Implicit Time (µV)	Amplitude (µV)
Inclusion a (n=24)	26 (18,5-32)	3,25 (11-17,7)	14 (11,5-18,5)	75 (50,85-55)	2,5 (1,9-3,35)	88 (91,8-11)	1 (-3,8;-2,15)
Week 4 a (n=17)	13 (7,5-26,25)	8 (5,75-13,88)	9 (3,75-13,75)	4,4 (50,63-56,2)	75 (1,83-3,58)	85 (94,34-10)	0 (-4,06;-2,36)
Week 8 a (n=15)	10 (3,5-13,75)	5,5 (2,6-10,4)	6 (3-7)	4 (51,98-56,2)	45 (2,26-3,99)	8 (92,04-11)	5 (-4,31;-2,44)
Week 12 a (n=15)	11 (-5,25-16)	6 (4,1-8,6)	4 (2,25-6,75)	05 (49,95-56,2)	45 (1,75-2,75)	2 (92,01-11)	5 (-3,91;-2,85)
	P-value	P-value	P-value	P-value	P-value	P-value	P-value
Incl.-W04 b	0.0078	0.0197	0.0108	0.18	0.46	0.11	0.89
Incl.-W08 b	0.0001	0.0014	0.00001	0.26	0.52	0.28	0.79
Incl.-W12 b	0.0002	0.0005	0.00001	0.32	0.89	0.41	0.92
W04-W08 b	0.281	0.2121	0.0635	0.66	0.93	0.62	0.98
W04-W12 b	0.3348	0.1558	0.0427	0.82	0.2	0.24	0.87
W08-W12 b	0.787	0.7712	0.617	0.89	0.61	0.68	0.85

@

Quantitative variable represented as median and interquartile range ^a

Mann-Whitney U test ^b