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Oscillatory potentials abnormalities in regular cannabis users: Amacrine cells dysfunction as a marker of central dopaminergic modulation

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ABSTRACT

Background: Cannabis is a neuromodulating substance that acts on central synaptic transmission. Regular cannabis use induces a decreased capacity for dopamine synthesis in the brain. The retina is considered an easy means of investigating dysfunctions of synaptic transmission in the brain. We have previously studied the impact of regular cannabis use on retinal function. Using the N95 wave of the pattern electroretinogram, we found a 6 ms-delayed ganglion cells response. Using the b-wave of the photopic flash electroretinogram, we found a 1 ms-delayed bipolar cells response. Here, we investigated amacrine cells function because these cells are located between the bipolar cells and the ganglion cells and contribute to amplifying the signal between these two layers of the retina. We tested the effect of regular cannabis use on these retinal dopaminergic cells. We assessed the role of these cells in amplifying the delay observed previously.

Methods: We recorded dark-adapted 3.0 flash ERG oscillatory potentials in 56 regular cannabis users and 29 healthy controls. The amplitude and implicit time of OP1, OP2, OP3 and OP4 were evaluated.

Results: Cannabis users showed a significant decrease in OP2 amplitude ($p = 0.029$, Mann-Whitney test) and OP3 amplitude ($p = 0.024$, Mann-Whitney test). No significant difference was found between the groups for OP1 and OP4 amplitude or for the implicit time of oscillatory potentials.

Conclusions: These results reflect the impact of regular cannabis use on amacrine cells function. They highlight abnormalities in dopaminergic transmission and are similar to those found in Parkinson's disease. Oscillatory potentials could be used as markers of central dopaminergic modulation.

1. Introduction

Cannabis is a major public health concern throughout the world. It is the most prevalent addictive illicit drug (Guttmannova et al., 2017). The main psychoactive substance in cannabis, tetra-hydro-cannabinol (THC), is known to act on the central nervous system (Broyd et al., 2016). This effect is mediated through the modulation of synaptic transmission in brain neurons (Bossong and Niesink, 2010). In particular, the glutamatergic and dopaminergic signaling pathways are the main synaptic transmission pathways affected by regular use of cannabis (Colizzi et al., 2016; Sami et al., 2015). As an example, cannabis is responsible for an excessive rate of glutamatergic synapsis, through the blockade of the CB1 presynaptic endocannabinoid receptors, and this leads to cell apoptosis (Schwitzer et al., 2015). Among regular cannabis users, it also leads to reduced capacity for dopamine synthesis in the brain (Bloomfield et al., 2016).

The retina is a forward projection of the brain, since it is anatomically and developmentally an extension of the central nervous system (Hoon et al., 2014). The retina is composed of successive layers of neurons with similar properties to brain neurons (London et al., 2013). These neurons are endowed with neurotransmitter signaling pathways such as the dopaminergic and glutamatergic pathways, which are also

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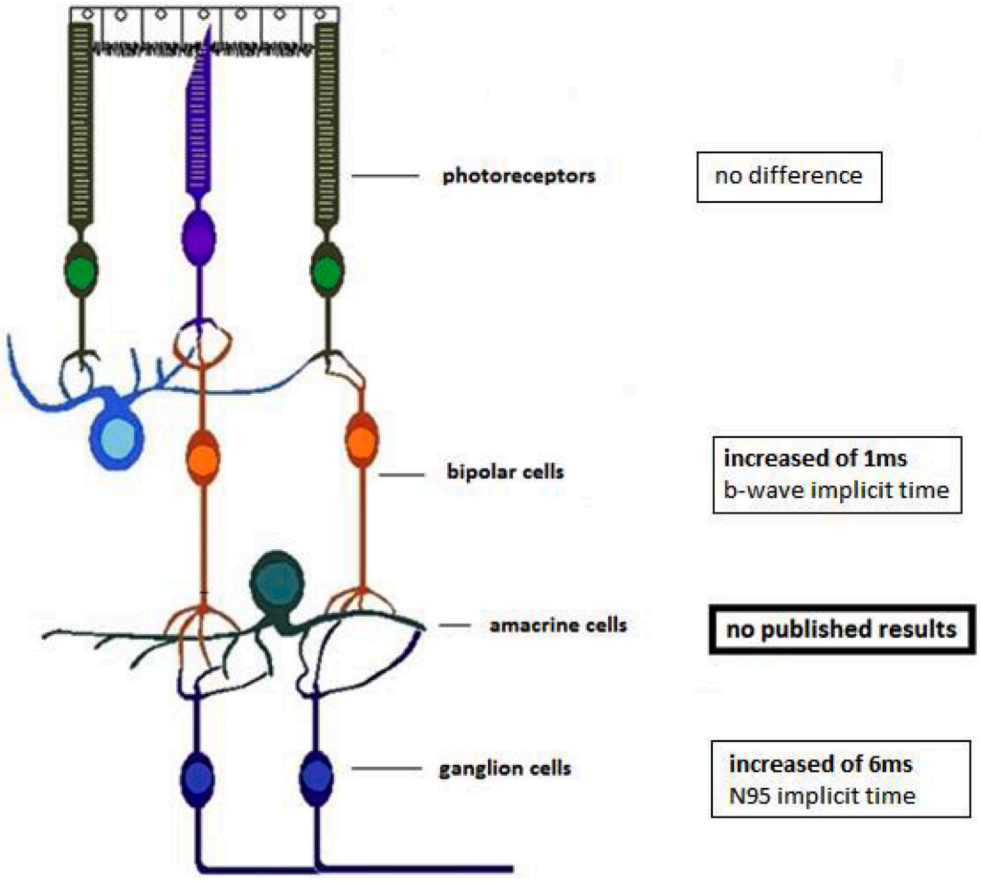

Fig. 1. Schematic organization of the retina with the results of previous studies studying the effect of regular cannabis use on retinal processing compared with controls.

found in brain neurons (Dowling et al., 1978; Brandon and Lam, 1983). The human retina has a functional endocannabinoid system that includes receptors, ligands and enzymes (Schwitzer et al., 2016). This system is involved in the modulation of neurotransmitter release in the retina (Schwitzer et al., 2019a). In light of this, we previously used the retina as an indirect means of determining the impact of regular cannabis use on brain neurotransmission (Schwitzer et al., 2017a; Schwitzer et al., 2019b; Lucas et al., 2019).

To begin with, we studied the final, more integrated layer of the retina, the retinal ganglion cells (Schwitzer et al., 2017b). Using the N95 of the pattern electroretinogram, we found a delayed retinal ganglion cells response, as shown by a 6 ms delay in the transmission of action potentials by the retinal ganglion cells. Then, using the b-wave of the ERG under photopic conditions, we also demonstrated a 1 ms-delayed retinal cone bipolar cells response (Schwitzer et al., 2018).

The transmission of electrical signals between the bipolar and the ganglion cells is amplified by the amacrine cells, however (Fig. 1). This may explain the six-fold increase in the delay between these two layers. The amacrine cells are interneurons located in the retinal inner nuclear layer between the bipolar and the ganglion cells. They form synapses between the axon terminals of bipolar cells and the dendrites of ganglion cells. Amacrine cells have a functional endocannabinoid system that includes cannabinoid CB1 receptors and ligands (Bouchard et al., 2016). Interestingly, amacrine cells function is influenced by dopaminergic transmission (Witkovsky, 2004). Amacrine cells have D1 and D2 dopaminergic receptors (Popova, 2014). They can be studied with oscillatory potentials (OP), small rhythmic wavelets superimposed on the ascending b-wave of the flash ERG. After filtering to enhance their amplitude, four wavelets can be distinguished, identified as OP1, OP2, OP3 and OP4. The generation of these wavelets involves dopamine (Wachtmeister, 1998). In this study, we investigated amacrine cells function to develop a better understanding of the mechanism responsible for the amplified delay between bipolar and ganglion cells response. We assume an effect of regular cannabis use on the amacrine dopaminergic system which may be responsible for the amplified delay in retinal cells response.

The aim of this study is to investigate amacrine cells by means of oscillatory potentials in regular cannabis users compared to healthy controls. We hypothesized an effect of regular cannabis use on amacrine cells function.

2. Material and methods

2.1. Population and ethics statement

Regular cannabis users (n = 56) and matched healthy drug naive controls (n = 29) were recruited among the general population via a special press campaign and data were collected from February 11, 2014 to June 30, 2016. Prior to taking part in the study, volunteers provided their detailed psychoactive drug and medical history, underwent a full psychiatric evaluation, and signed consent forms detailing all aspects of the research. All participants received payment in the form of €100 in gift vouchers. The study protocol met the requirements of the Helsinki Declaration and was approved by the Ethics Committee of Nancy University Hospital. This study is part of a bigger project, Causa Map, which is researching the impact of regular cannabis use on the visual system. All participants also underwent neuropsychological assessments and EEG was recorded while performing several visual tasks.

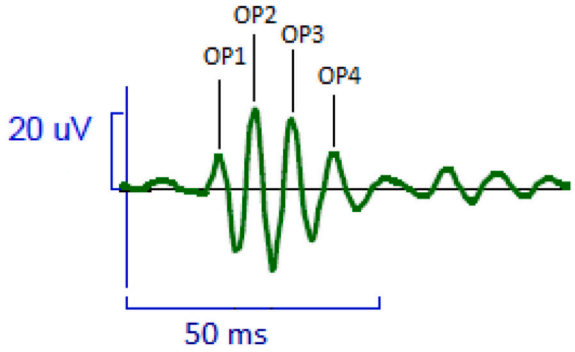

Fig. 2. Typical trace of a scotopic oscillatory potential flash ERG.

2.2. Inclusion criteria, clinical and biological assessments

The inclusion criteria for the cannabis group was regular cannabis use equivalent to at least 7 cannabis consumptions per week over the past month, a positive urine toxicology screen for THC metabolites, no other illicit substance use in the past month, a negative urine toxicology screen for other illicit substances, and no DSM-IV diagnosis of Axis I disorders. Since tobacco is regularly mixed with cannabis in joints, cannabis users may meet the criteria for tobacco dependence according to the Fagerström test. Cannabis users were required to have abstained from cannabis use for at least 12 h to avoid acute cognitive dysfunction caused by cannabis use. The inclusion criteria for the healthy control subjects were no history of illicit substance use, a negative urine toxicology screen for the metabolites and the other illicit drugs tested, and no history of DSM-IV diagnosis Axis I psychiatric disorders. All the participants were aged 18 to 35 years, had no history of neurological disease, no family history of schizophrenia or bipolar disorders, and were medication-free except for oral contraceptives in the case of women. They had no history of ophthalmological disease except for corrective refractive errors. All fared normally in an ophthalmic evaluation, which included visual acuity and a fundocopic examination. Importantly, visual acuity measured with the monomer scale was at least 10/10 in each eye for all participants. None of the participants reported visual symptoms, and none was found to have any media opacities. 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 (M.I.N·I) was used to assess current and past history of psychiatric diseases and substance use. In addition, the Cannabis Abuse Screening Test (CAST), Fagerström test and AUDIT were performed to assess use, abuse and dependance with respect to cannabis, tobacco and alcohol respectively. They extent of cannabis use was clinically assessed in an interview and a questionnaire as follow: age when regular cannabis use began, total years of cannabis use, average number of joints smoked daily and weekly over the past month and average number of grams smoked weekly. In order to obtain objective confirmation of cannabis consumption, urine drug screens (nal von minden, Moers, Germany) were performed for cannabis, buprenorphine, benzodiazepines, cocaine, opiates, amphetamines and methadone immediately before electroretinogram testing.

2.3. Experimental protocol

Electrical signals were recorded simultaneously from both eyes (averaged for analysis), and dilated pupils (tropicamide 0.5%), with DTL electrodes (metrovision, Pérenchies, France) placed at the bottom of the conjunctival sac. The reference electrode was placed on the forehead. Pupil size was noted before and after dark-adapted ERG recordings and remained systematically constant throughout the testing period. Ground and reference electrodes were attached to the forehead and external canthi. Analysis was performed with the experimenter blind to the status of the subject being recorded (cannabis user or control). It was performed according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standards for flash ERG (McCulloch et al., 2015).

Flash ERG was performed under scotopic conditions with dark-adapted 3.0 oscillatory potentials as generally used in the literature (Marmor et al., 2004) and in the ISCEV standards (McCulloch et al., 2015). It enables interaction between the rod and cone system, induces a steady state of adaptation and provides consistent, reproducible recording conditions (Wachtmeister, 1998). Participants were positioned 30 cm from the screen. They were dark-adapted for a period of 20 min before dark-adapted 3.0 ERG oscillatory potentials were performed, managed by the MonPackONE, which measured the oscillatory potentials corresponding to the electrical activity of the amacrine cells. At least eight responses were recorded for each participant.

2.4. Analysis

Four main components are usually described in oscillatory potentials: OP1, OP2, OP3 and OP4 (Fig. 2). Two main parameters are derived from the OP, conventionally known as amplitude in microvolts (μV) and implicit time in milliseconds (ms). The OP1 amplitude was measured from the baseline to the peak of the wave. The OP2, OP3 and OP4 amplitudes were measured from the trough of the preceding wave to the peak of the corresponding wave. Implicit time denotes the time taken to reach the maximum amplitude of each wave. An overall index, the sum of the OP1, OP2 and OP3 amplitudes, was also analyzed.

2.5. Statistical analysis

Variables are presented as numbers or median and inter quartile range (IQR). Depending on the nature of the variables and the non-parametric distribution of quantitative variables, the Mann-Whitney test and the Khi square test were used to compare the two groups where appropriate. For correlation analysis, Spearman's rank correlation coefficient (Spearman's rho) was used. The relevant differences between the two groups involved OP2 amplitude, OP3 amplitude, years of education, AUDIT score and average number of occasions of alcohol use per week. To adjust the amplitude analysis according to years of education and alcohol use, multivariate analysis was planned. As average weekly alcohol use was strongly correlated with the AUDIT score (rho = 0.738; p = 0.0001), we used the AUDIT score in the analysis, presenting the lowest p value in the comparison of the two groups. As the amplitudes of OP2 amplitude and OP3 were strongly correlated (rho = 0.954; p = 0.0001), which is a relevant result in this study, only the OP3 amplitude, with the lowest p value, was used in the multivariate analysis. The logistic regression therefore included OP3 amplitude, years of education and the AUDIT score, with cannabis users and controls as the binary outcome variable. We used alpha < 0.05% for comparisons and to include variables in the multivariate analysis. Statistical analyses were performed using IBM-SPSS Statistics 22.0 (IBM corp.)

3. Results

3.1. Demographic and substance use characteristics

The demographic and substance use characteristics of the participants are described in Table 1. There was no relevant difference between the controls and the cannabis users in terms of age (p = 0.47) or gender (p = 0.53), but differences were noted between the groups in terms of years of education (p = 0.0001; lower in cannabis users) and alcohol use (higher in cannabis users; p = 0.0003 for average alcohol consumption/week; p = 0.0001 for AUDIT score). As tobacco is widely combined with cannabis in joints, 44 out of 56 cannabis users were also

Table 1
Demographic and substance use characteristics of the participants.

	Cannabis users (n = 56)	Controls (n = 29)	p-value
Gender (male/female)[a, d]	44/12	21/8	0.526
Age (years)[b, c]	23 (20.5–30)	24 (23–27)	0,466
Education (years)[b, c]	13 (12–14)	15 (14–16)	0.0001
Average number of AU/week[b, c]	4 (1,5–10)	1 (0–3)	0.0003
AUDIT scores[b, c]	7 (3,5–9,5)	3 (1–4)	0.0001
Fagerström test scores (n = 44)[b]	1 (0–3)	–	–
Average number of cigarettes/day[b]	4 (2 − 10)	–	–
Age of first cannabis use[b]	16 (15–17)	–	–
Total years of cannabis use[b]	7 (5–14)	–	–
Average number of joints/week[b]	20 (14–30)	–	–
CAST scores[b]	4 (3–5)	–	–
Average number of grams of cannabis/week[b]	4,1 (3 − 10)	–	–

[a] Categorical variable represented as frequencies.
[b] Quantitative variable represented as median and interquartile range.
[c] Mann-Whitney U test.
[d] Chi-Square test.

tobacco smokers, whereas all the controls were non-smokers. According to the Fagerström test, 27 out of 44 cannabis users were not dependent on tobacco, 12 were slightly dependent, 4 were moderately dependent and 1 was highly dependent.

3.2. Dark-adapted 3.0 ERG oscillatory potential

The oscillatory potential parameters are described in Table 2. The median and interquartile range of OP2 amplitude was 33.03 μV (27.43: 41.98) in the cannabis users versus 38.05 μV (34.60: 44.80) in the controls (Fig. 3). This difference was significant between groups (p = 0.029; Mann-Whitney test). The median and interquartile range of OP3 amplitude was 30.05 μV (25.83: 39.15) in the cannabis users versus 36.85 μV (31.95: 40.85) in the controls (Fig. 4). This difference was significant between groups (p = 0.024; Mann-Whitney test). The median and interquartile range of the sum of OP1, OP2 and OP3 amplitudes was 72.80 μV (62.60: 95.15) in the cannabis users versus 86.15 μV (78.00, 95.05) in the controls. This difference was significant between groups (p = 0.040; Mann-Whitney test). There were no differences between groups for the OP1 and OP4 amplitudes (p = 0.254 and p = 0.653 respectively). There were no differences in implicit time for OP1, OP2, OP3 and OP4 (p = 0.502, p = 0.805, p = 0.846 and p = 0.820 respectively). The OP2 and OP3 amplitudes were strongly correlated (rho = 0.954; p = 0.0001) (Fig. 5).

The logistic regression with cannabis users and controls as the binary outcome variable included OP3 amplitude, years of education and the AUDIT score. The results are as follows: regression was statistically significant (p = 0,0001); Hosmer-Lemeshow test (p = 0.647). OP3 amplitude remained significant according to AUDIT and years of education (p = 0.004) (Table 3). The classification results in 84.7% of subjects being correctly classified by the model (79.3% of controls, 23/29; 87.5% of cannabis users, 49/56).

4. Discussion

We found a decrease in OP2 amplitude around 5 μV, a decrease in OP3 amplitude around 7 μV, and a decrease in the sum of OP1, OP2 and OP3 amplitudes around 13 μV–mainly corresponding to the sum of the decreased OP2 and OP3 amplitudes–in regular cannabis users compared to the controls, with no modification in implicit time. OP2 and OP3 are the major components of oscillatory potentials since they expressed the highest oscillatory potential amplitude. The final OP4 oscillatory potential is smaller than OP2 and OP3 (McCulloch et al., 2015). The first oscillatory potential, OP1, may derive from a different origin within the retina (Speros and Price, 1981). We found modifications in oscillatory potential amplitude; this is relevant according to the literature and indeed, oscillatory potential amplitude is the only parameter commonly measured in oscillatory potentials (Wachtmeister, 1998).

Here, the decreased amplitude of OP2 and OP3 in regular cannabis users could be seen as the consequence of regular cannabis use on amacrine cells function. As the function of these cells is influenced by dopaminergic transmission, we assume an effect of regular cannabis use on the retinal dopaminergic signaling pathway. The main psychoactive component detected in cannabis–THC–is a neuromodulator substance that acts on dopaminergic transmission (Bloomfield et al., 2016). Several studies using positron emission tomography have highlighted reduced dopamine synthesis capacity in regular cannabis users (Bloomfield et al., 2014), which may be responsible for the decreased oscillatory potential amplitude in our study. Other results also showed reduced dopamine transporter density in regular cannabis users (Leroy et al., 2012), altered dopamine receptor signal transduction and structural abnormalities in dopaminergic neurons (Spiga et al., 2010). These findings are consistent with hypoactivity of dopaminergic transmission in regular cannabis users, which has already been seen in the retina, in the amacrine cells layer. In regular cannabis use, hypofunction of the amacrine cells dopaminergic pathway can occur, as observed in the decreased amplitude of oscillatory potentials.

As cannabis is a dopaminergic modulator, we can confirm that retinal oscillatory potentials may be good indicators of modulation of central dopaminergic pathways. Amacrine cells function, as reflected in oscillatory potentials, is influenced by dopaminergic transmission (Marmor et al., 1988). Previous studies have shown a correlation between modifications of oscillatory potentials and central dopaminergic transmission. For example, reserpine, a dopamine depleter, reduces oscillatory potential amplitude and L-Dopa, a dopamine precursor, reverses this effect (Orlando Gutiérrez and Spiguel, 1973; Citron et al., 1985). Haloperidol, an antipsychotic drug that blocks dopaminergic transmission, also decreases oscillatory potential amplitude

Table 2
Dark-adapted 3.0 oscillatory potentials ERG parameters.

	Cannabis users (n = 56)	Controls (n = 29)	p-value
OP1 Implicit Time (ms)[a, b]	14.90 (14.60:15.20)	14.90 (14.60:15.20)	0.502
OP1 Amplitude (μV)[a, b]	14.13 (10.93:16.03)	13.90 (13.15:16.95)	0.254
OP2 Implicit Time (ms)[a, b]	21.85 (21.40:22.15)	21.70 (21.40:22.30)	0.805
OP2 Amplitude (μV)[a, b]	33.03 (27.43:41.98)	38.05 (34.60:44.80)	0.029
OP3 Implicit Time (ms)[a, b]	28.50 (28.05:29.10)	28.50 (28.20:29.10)	0.846
OP3 Amplitude (μV)[a, b]	30.05 (25.83:39.15)	36.85 (31.95:40.85)	0.024
OP4 Implicit Time (ms)[a, b]	35.80 (35.25:37.00)	36.10 (35.50:37.30)	0.820
OP4 Amplitude (μV)[a, b]	17.58 (13.83:22.23)	18.50(13.95:21.70)	0.653
Sum of amplitudes (OP1 + OP2 + OP3)[a, b]	72.80(62.60:95.15)	86.15(78.00:95.05)	0.040

[a] Quantitative variable represented as median and interquartile range.
[b] Mann-Whitney U test.

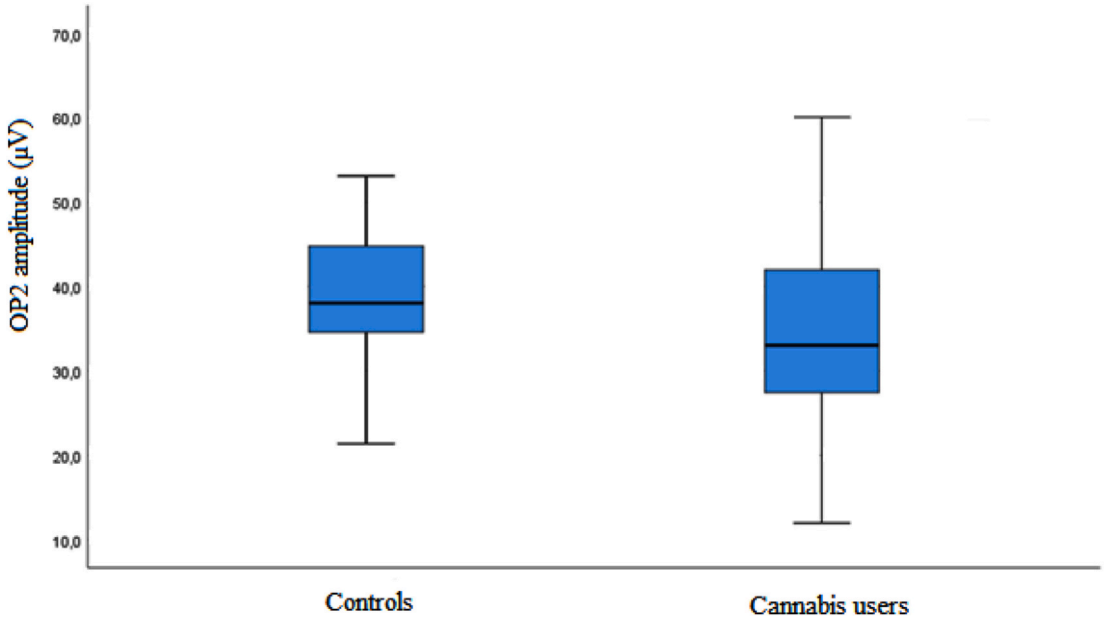

Fig. 3. Box plot of oscillatory potentials 2 amplitude with median and interquartile range in regular cannabis users (n = 56) and controls (n = 29).

(Wachtmeister, 1981). Interestingly, our results confirm previous observations and can also be viewed as a direct consequence of a decreased central level of dopamine.

In Parkinson's disease, a neurological disorder resulting in decreased central dopamine, patients with early-stage disease showed a decrease in dark-adapted OP2 and OP3 amplitudes as well as in the sum of OP1, OP2 and OP3 amplitudes (Nowacka et al., 2015). Interestingly, the results are similar to our findings in regular cannabis users, which showed a decreased level of dopamine. In other studies, a decrease in OP2 amplitude was also found in patients with Parkinson's disease compared with controls (Kupersmith et al., 1982; Gottlob et al., 1987). In schizophrenia, a mental illness resulting in enhanced central dopaminergic transmission, an increase in oscillatory potential amplitude was found (Raese et al., 1982). As a consequence, oscillatory potential amplitude is enhanced when the central level of dopamine is increased and reduced when the central level of dopamine is decreased. We suggest oscillatory potentials as a marker of the central level of dopamine.

Our study was performed under scotopic conditions and involved a mixed rod-cone response. Dopaminergic release under such conditions is reduced compared with photopic conditions, in which dopaminergic release is at its highest. Although this study was not performed under optimal light conditions, we still observed significant results, which reinforces the relevance of these results. Since tobacco is frequently combined with cannabis in joints, our previous studies statistically eliminated the effect of tobacco on the retinal modulations observed in cannabis users (Schwitzer et al., 2017b; Schwitzer et al., 2018).

One approach to follow up on this study would be to implement a control group of tobacco smokers, to separate the effect of each substance on retinal function and specifically on oscillatory potentials. We

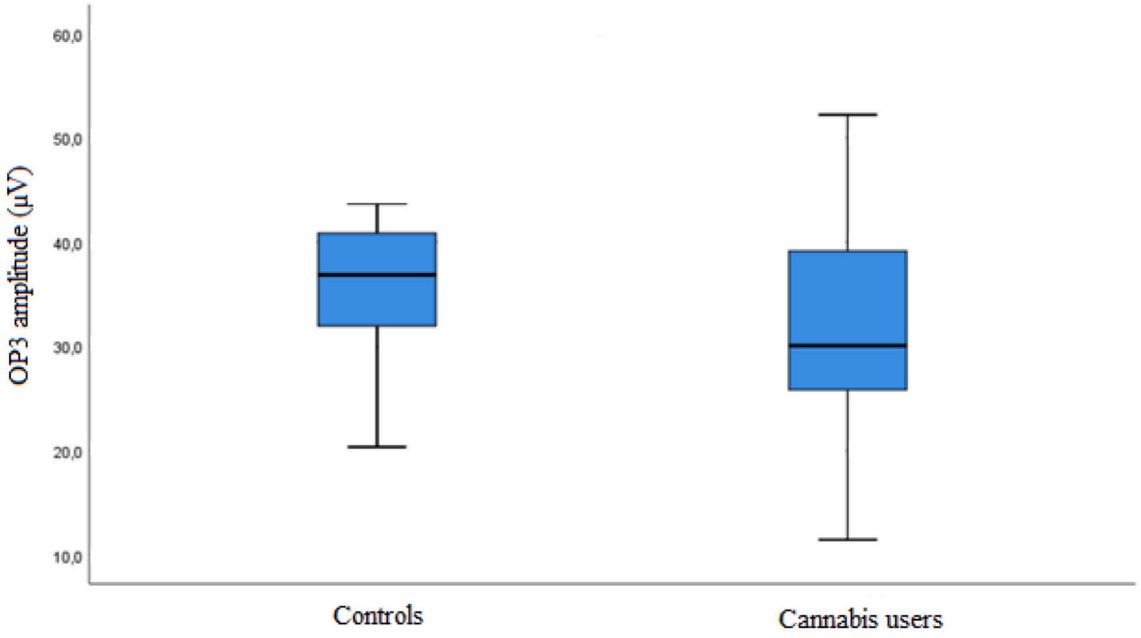

Fig. 4. Box plot of oscillatory potentials 3 amplitude with median and interquartile range in regular cannabis users (n = 56) and controls (n = 29).

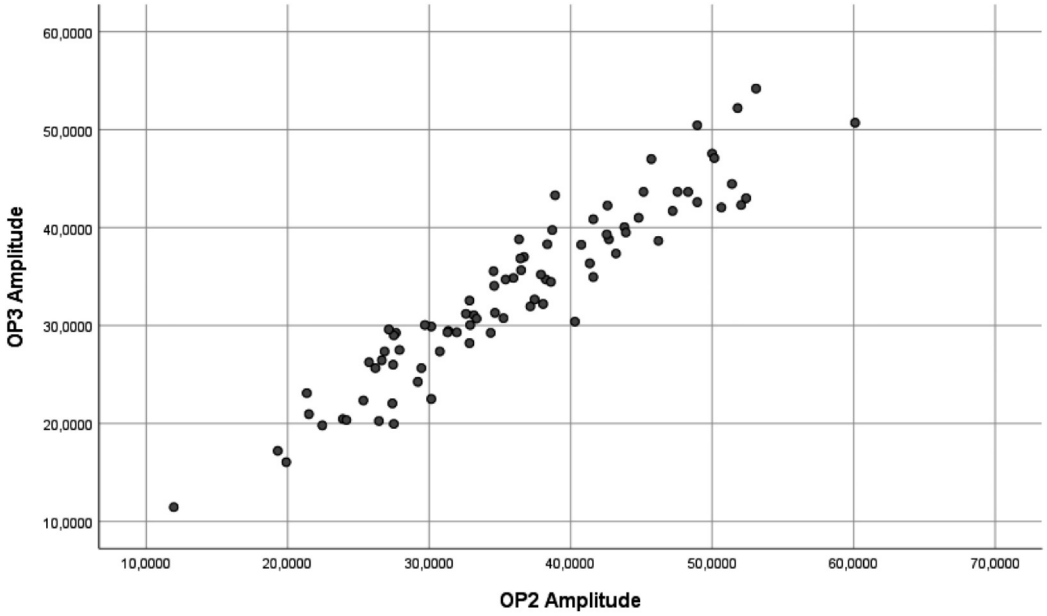

Fig. 5. Correlation: relationship between OP2 and OP3 amplitude.

Table 3
Logistic regression between OP3 amplitude, AUDIT score and education years CP.

			Confidence interval 95% for OR	
	Sig	OR	Inferior	Superior
AUDIT score	0.000	1.517	1.208	1.906
Education years CP	0.000	0.447	0.288	0.694
OP3 amplitude	0.004	0.876	0.801	0.959

could also use a flash 3.0 ERG under mesopic or scotopic conditions to analyze the oscillatory potentials in optimal light conditions, to enhance our study.

5. Conclusion

In summary, regular cannabis users showed decreased amplitude in OP2 and OP3 wave with the oscillatory potentials 3.0 flash ERG. Theses abnormalities are underpinned by dysfunctions in the dopaminergic amacrine cells of the retina. The retina is a crucial site for investigation of brain synaptic transmission abnormalities. Amacrine cells could be used as a marker of central dopaminergic modulation and a way to study dopaminergic diseases.

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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 the Ethics Committee of Nancy University Hospital. This study is part of a bigger project, Causa Map, which is researching the impact of regular cannabis use on the visual system.

Declaration of Competing Interest

All the authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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