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Association Between Regular Cannabis Use and Ganglion Cell Dysfunction

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IMPORTANCE Because cannabis use is a major public health concern and cannabis is known to act on central neurotransmission, studying the retinal ganglion cells in individuals who regularly use cannabis is of interest.

OBJECTIVE To determine whether the regular use of cannabis could alter the function of retinal ganglion cells in humans.

DESIGN, SETTING, AND PARTICIPANTS For this case-control study, individuals who regularly use cannabis, as well as healthy controls, were recruited, and data were collected from February 11 to October 28, 2014. Retinal function was used as a direct marker of brain neurotransmission abnormalities in complex mental phenomena.

MAIN OUTCOMES AND MEASURES Amplitude and implicit time of the N95 wave on results of pattern electroretinography.

RESULTS Twenty-eight of the 52 participants were regular cannabis users (24 men and 4 women; median age, 22 years [95% CI, 21-24 years]), and the remaining 24 were controls (20 men and 4 women; median age, 24 years [95% CI, 23-27 years]). There was no difference between groups in terms of age (P = .13) or sex (P = .81). After adjustment for the number of years of education and alcohol use, there was a significant increase for cannabis users of the N95 implicit time on results of pattern electroretinography (median, 98.6 milliseconds [95% CI, 93.4-99.5]) compared with controls (median, 88.4 milliseconds [95% CI, 85.0-91.1]), with 8.4 milliseconds as the median of the differences (95% CI, 4.9-11.5; P < .001, Wald logistic regression). A receiver operating characteristic curve analysis (area under the curve, 0.84 [95% CI, 0.73-0.95]; P < .001) revealed, for a cutoff value of 91.13 milliseconds, a sensitivity of 78.6% (95% CI, 60.5%-89.8%) and a specificity of 75.0% (95% CI, 55.1%-88.0%) for correctly classifying both cannabis users and controls in their corresponding group. The positive predictive value was 78.6% (95% CI, 60.5%-89.8%), and the negative predictive value was 75.0% (95% CI, 55.1%-88.0%).

CONCLUSIONS AND RELEVANCE Our results demonstrate a delay in transmission of action potentials by the ganglion cells in regular cannabis users, which could support alterations in vision. Our findings may be important from a public health perspective since they could highlight the neurotoxic effects of cannabis use on the central nervous system as a result of how it affects retinal processing.

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The retina is an easy-to-access anatomic and developmental extension of the central nervous system,[1] which several research teams have suggested as being a crucial site for investigating human central synaptic transmission in complex mental phenomena.[2-12] Among these phenomena, the increasing use of cannabis represents an ever-growing public health challenge,[13] but little is known about the effect of cannabis use on human neural synaptic transmission. Retinal processing could constitute a breakthrough on this issue.

This study aimed to assess the stage of the retinal ganglion cells (RGCs) because it is particularly relevant to study the effect of regular cannabis use on human neural synaptic transmission. Retinal ganglion cells are the last and most integrated stage of retinal processing and the first retinal stage providing visual information in the form of action potentials, such as is found in the brain.[14] The endocannabinoid system is detected in RGCs and is involved in RGC synaptic transmission.[3,5,15] For example, in animals, cannabinoid agonists reduce glutamate release in rodent RGCs.[16,17] In humans, glutamate is also a main transmitter involved in retinal physiologic structure and in the vertical transmission of retinal information.[18,19] The action of cannabis on central glutamatergic transmission[20] may thus disturb RGC function in humans. To verify this hypothesis, we used a standard electrophysiological measurement called pattern electroretinography (PERG),[21] which involved averaging a high number of responses, thereby ensuring reproducibility of the results.[22] With PERG, the best marker of RGC function is a negative wave—the N95 wave—2 parameters of which are usually known as the amplitude and the implicit time, which denotes the time needed to reach the maximal amplitude of N95.[21,22]

We describe the results of the first study, to our knowledge, to assess the effect of regular cannabis use on human RGC function. Given the role of the cannabinoid system in regulating RGC synaptic transmission, we hypothesized that the RGC response can be affected by regular cannabis use.

Key Points

Question What is the effect of regular cannabis use on the function of retinal ganglion cells?

Findings In this case-control study of 28 individuals who regularly used cannabis and 24 controls, a large delay in retinal information processing was found in regular cannabis users compared with controls based on an increase in N95 implicit time on results of pattern electroretinography.

Meaning Although this study is preliminary and not designed to determine cause and effect, the findings suggest that retinal function might be used as a marker of brain neurotransmission abnormalities in cannabis users.

Methods

Study Population

Twenty-eight individuals who regularly used cannabis and 24 matched, healthy, drug-naive controls were recruited among the general population via a special press campaign, and data were collected from February 11 to October 28, 2014. Before 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 (approximately US $110) in gift vouchers. The study protocol met the requirements of the Declaration of Helsinki[23] and was approved by the Nancy University Hospital Ethics Committee. This study is part of a larger project, Causa Map, which is researching the effect of regular cannabis use on the visual system. All participants also underwent neuropsychological assessments and electroencephalography while they performed several visual tasks. Given the innovative nature of these measurements, the protocol provides an intermediate analysis that is focused on RGC functioning.

The inclusion criteria for the cannabis group were regular cannabis use at the rate of at least 7 cannabis consumptions per week during the past month, positive results for tetrahydrocannabinol metabolites on a urine toxicology test, no other illicit substance use in the past month, negative results for other illicit substances on a urine toxicology test, and no *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) diagnosis of Axis I disorders. Since tobacco is regularly mixed with cannabis in cigarettes (joints), cannabis users may meet the criteria for tobacco dependence according to the Fagerström test. Cannabis users were required to present with at least 12 hours of abstinence of cannabis use so that there were no acute cognitive dysfunctions owing to cannabis use.

Inclusion criteria for the healthy controls were no history of illicit substance use, negative results for tetrahydrocannabinol metabolites and other illicit drugs on a urine toxicology test, and no history of *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) diagnosis of Axis I psychiatric disorders. All participants were aged 18 to 35 years, had no history of neurologic disease, no family history of schizophrenia or bipolar disorders, and were not taking medication except for oral contraceptives in the case of women. They had no history of ophthalmologic disease except for corrected refractive errors. All participants had normal results on ophthalmic evaluation, which included visual acuity and a fundoscopic examination. More important, 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, and none was found to have any media opacities. If participants reported alcohol dependence according to their score in the Alcohol Use Disorders Identification Test (AUDIT), they were excluded from the study.

Clinical and Biological Assessments

The Mini-International Neuropsychiatric Interview was administered to assess current and past history of psychiatric diseases and substance use. In addition, the Cannabis Abuse Screening Test, Fagerström Test, and AUDIT were performed to assess use, abuse, or dependence with respect to cannabis, tobacco, and alcohol, respectively. The extent of cannabis use

Table. Demographic and Substance Use Characteristics of the Participants

Characteristic	Value[a]	
	Cannabis Users (n = 28)	Controls (n = 24)
Male, No. (%) [95% CI]	24 (86) [69-94]	20 (83) [64-93]
Age, y	22 (21-24)	24 (23-27)
Education, y	13.5 (13-14)	15 (14-16)
No. of alcohol uses per week	4 (3-6)	1 (0-2)
Alcohol Use Disorders Identification Test score	6 (4-10)	3 (1-4)
Fagerström Test score (n = 26)	1 (0-2)	NA
No. of cigarettes per day	3.5 (2-6)	NA
Age of first cannabis use, y	16 (16-17)	NA
Total years of cannabis use	6 (5-12)	NA
No. of joints per week	20 (14-21)	NA
Cannabis Abuse Screening Test score	4 (3-5)	NA
No. of grams of cannabis per week	5 (3-6)	NA

Abbreviation: NA, not applicable.

[a] Data are presented as median (95% CI) unless otherwise indicated.

was clinically assessed in an interview and a questionnaire as follows: age when regular cannabis use began, total years of cannabis use, average number of joints smoked daily and weekly during the past month, and average number of grams of cannabis smoked weekly (**Table**). To obtain objective confirmation of cannabis consumption, urine drug tests (nal von minden) were performed for cannabis, buprenorphine, benzodiazepines, cocaine, opiates, amphetamines, and methadone immediately before PERG testing.

PERG Measurements

Pattern electroretinography measurements were compiled according to the International Society for Clinical Electrophysiology of Vision standards for PERG.[21] The MonPackOne system (Metrovision) was used for stimulation, recording, and analysis. Electrical signals were recorded simultaneously from both eyes (averaged for analysis) on nondilated pupils, with Dawson-Trick-Litzkow electrodes (Metrovision) placed at the bottom of the conjunctival sac. Ground and reference electrodes were attached to the participant's forehead and external canthi. A black-and-white reversible checkerboard was used, with 0.8° check size, 93.3% contrast level, 100 candela/m^2 constant luminance white area, and 4 reversals per second. The participant was positioned 1 m 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. Pattern electroretinography data were analyzed with Moniteur Ophthalmique (Metrovision). Pattern electroretinography analysis was performed with the experimenter masked to the status of the participant being recorded (ie, cannabis user or control). Two main components are usually described on a typical PERG trace: an electropositive component, P50, followed by an electronegative component, N95. The electronegative component (N95) is attributed to the RGC and reflects their response.[21] Two main parameters are derived from N95, known by convention as the amplitude measured in microvolts and the implicit time measured in milliseconds. The N95 amplitude is measured from the trough of the N95 wave to the peak of the P50 wave. Implicit time denotes the time taken to reach the maximum N95 amplitude.

Statistical Analysis

Depending on the nonparametric distribution of several variables included in the analyses, the Mann-Whitney test, χ^2 test, and Spearman rank correlation test were used when appropriate to compare the 2 groups or to test the association between variables. Among all the variables and in this particular context, the relevant differences between the 2 groups involved N95 implicit time, years of education, AUDIT score, and average number of alcohol uses per week. To analyze N95 implicit time between the two groups, we used logistic regression to adjust for years of education and alcohol use. As average alcohol use per week was correlated with the AUDIT score, we kept the AUDIT score in the analysis. The logistic regression included N95 implicit time, years of education, and the AUDIT score, with cannabis users and controls as the binary outcome variable. A receiver operating characteristic curve was applied to the N95 implicit time values to estimate the sensitivity and specificity of cutoff values between regular cannabis users and controls. Since this study is a pilot study based on preliminary data, we chose to use a conservative level of significance in comparison with $\alpha<.025$. Statistical analyses were performed using IBM SPSS Statistics, version 22.0 (IBM Corp).

Results

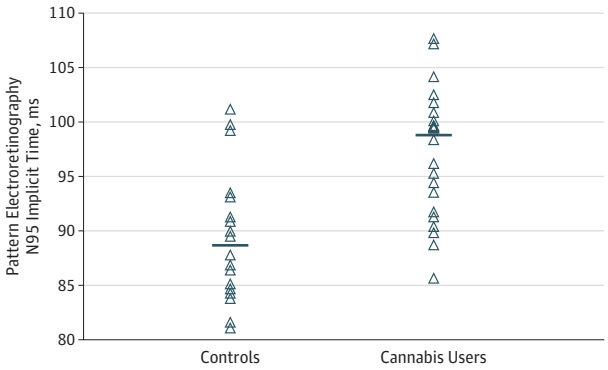
Demographic and Substance Use Characteristics

The demographic and substance use characteristics of the participants are described in the Table. There was no significant difference between controls and cannabis users for median age (cannabis users, 22 years [95% CI, 21-24]; controls, 24 years [95% CI, 23-27]; $P = .13$) or sex (cannabis users, 24 men [86%] and 4 women [14%]; controls, 20 men [83%] and 4 women [17%]; $P = .81$), but differences were noted between the groups in terms of average years of education (cannabis users, 13.5 years [95% CI, 13-14]; controls, 15 years [95% CI, 14-16]; $P = .02$), average number of alcohol uses per week (cannabis users, 4 [95% CI, 3-6]; controls, 1 [95% CI, 0-2]; $P = .002$), and median AUDIT score (cannabis users, 6 [95% CI, 4-10]; controls, 3 [95% CI, 1-4]; $P < .001$). Because tobacco is widely mixed with cannabis in joints, 21 of 28 cannabis users were also tobacco smokers, whereas all members of the control group were nonsmokers. More important, cannabis users were not dependent on tobacco, apart from 1 individual who was only mildly dependent.

PERG Parameters

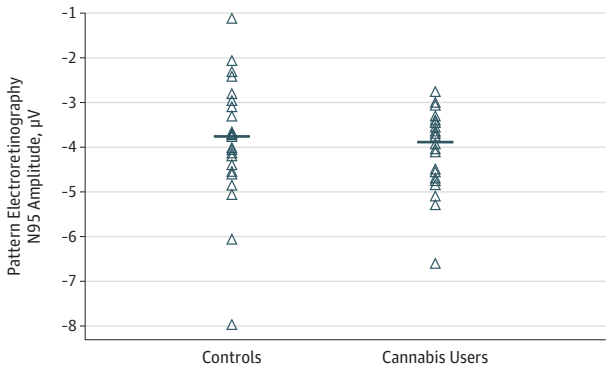
We found an increase in N95 implicit time on the results of PERG in the 28 regular cannabis users (median, 98.6 milliseconds [95% CI, 93.4-99.5]) compared with the 24 healthy controls (median, 88.4 milliseconds [95% CI, 85.0-91.1]), with 8.4

Figure 1. Dot Plot of Pattern Electroretinography N95 Implicit Time for Cannabis Users and Controls



For controls: n = 24; median implicit time, 88.4 milliseconds (95% CI, 85.0-91.1). For cannabis users: n = 28; median implicit time: 98.6 milliseconds (95% CI, 93.4-99.5). Median of the differences between the 2 groups: 8.4 milliseconds (95% CI, 4.9-11.5; $P < .001$, Mann-Whitney test). The black horizontal lines indicate medians.

Figure 2. Dot Plot of Pattern Electroretinography N95 Amplitude for Cannabis Users and Controls



For controls: n = 24; median amplitude, −3.78 μV (95% CI, −4.45 to −3.15). For cannabis users: n = 28; median amplitude, −3.90 μV (95% CI, −4.55 to −3.60; $P = .37$, Mann-Whitney test). The black horizontal lines indicate medians.

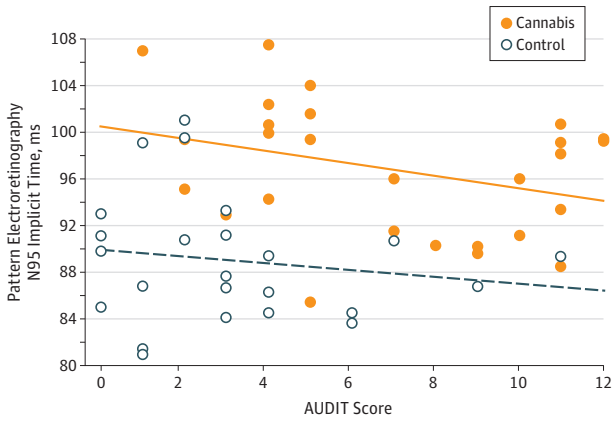
milliseconds as the median of the differences (95% CI, 4.9-11.5; $P < .001$, Wald logistic regression) (**Figure 1**). The median N95 amplitude was -3.90 μV (95% CI, -4.55 to -3.60) in cannabis users vs -3.78 μV (95% CI, -4.45 to -3.15) in controls ($P = .37$, Mann-Whitney test) (**Figure 2**).

The logistic regression was conducted with N95 implicit time, years of education, and the AUDIT score, with cannabis users and controls as the binary outcome variable. As average number of alcohol uses per week was correlated with the AUDIT score (Spearman rank correlation, 0.736; $P < .001$), we kept the AUDIT score ($P < .001$ for the difference between controls and cannabis users vs $P = .002$ for the average number of alcohol uses per week) in this analysis. The results of the logistic regression ($\chi^2 = 40.3$; $P < .001$; Hosmer Lemeshow $\chi^2 = 6.21$; $P = .62$; 86.5% of participants correctly classified in their respective group: 89% of cannabis users and 83% of controls) showed that N95 implicit time was significant (Wald $P = .001$), as was the AUDIT score (Wald $P = .008$), but years of education was not significant (Wald $P = .10$).

The N95 implicit time and AUDIT score were both significant between cannabis users and controls. The product AUDIT score × N95 implicit time (interaction) was not added to the model because it was too strongly correlated with the AUDIT score (Spearman rank correlation, 0.994; $P < .001$). We thus graphically investigated the interaction with 2 regression lines of N95 implicit time on the AUDIT score for controls and cannabis users (**Figure 3**). The 95% CI of the 2 slopes, which were both negative, overlapped, and the lines did not cross among the ranges of the observed values (controls, 0.299; [95% CI, -1.111 to 0.516]; cannabis users, -0.517; [95% CI, -1.114 to 0.078]).

Spearman rank correlations among all 52 participants between N95 implicit time and years of education, AUDIT score, and average number of alcohol uses per week were, respectively, -0.149 ($P = .29$), 0.093 ($P = .51$), and 0.125 ($P = .38$). Spearman rank correlations for the 28 cannabis users between N95 implicit time and number of cigarettes per day and number of packets of tobacco per year were, respectively, -0.191 ($P = .33$) and -0.165 ($P = .40$).

Figure 3. Interaction Between the Pattern Electroretinography N95 Implicit Time and Alcohol Use Disorders Identification Test (AUDIT) Score

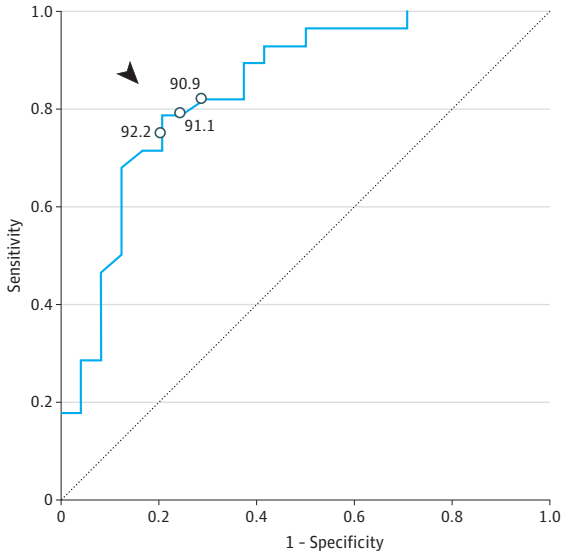


Linear regression lines of N95 implicit time on the AUDIT score for controls and cannabis users. The 95% CIs of the 2 negative slopes overlap, and the lines do not cross among the ranges of the observed values (controls, −0.299 [95% CI, −1.114 to 0.516]; cannabis users, −0.517 [95% CI, −1.111 to 0.078]).

Sensitivity and Specificity

A receiver operating characteristic curve was used to assess the best N95 implicit time cutoff value capable of discriminating between cannabis users and controls (area under the curve, 0.84; 95% CI, 0.73-0.95; $P < .001$). Results indicated that the cutoff value giving the best balance between sensitivity and specificity for regular cannabis users and controls was 91.13 milliseconds. Twenty-two of 28 regular cannabis users were above the cutoff, with an estimated sensitivity of 78.6% (95% CI, 60.5%-89.8%), whereas 18 of 24 controls were below the cutoff, with an estimated specificity of 75.0%

Figure 4. Receiver Operating Characteristic Curve Associated With N95 Implicit Time



Area under the curve = 0.84 (95% CI, 0.73-0.95; $P < .001$). For the cutoff value of 91.13 milliseconds (black arrow), 22 of 28 cannabis users are above the cutoff, with an estimated sensitivity of 78.6%, whereas 18 of 24 controls are below the cutoff, with an estimated specificity of 75.0%. For the cutoff value of 90.90 milliseconds, sensitivity = 82.1% and specificity = 70.8%; for the cutoff value of 92.23 milliseconds, sensitivity = 75.0% and specificity = 79.2%.

(95% CI, 55.1%-88.0%). Corresponding estimated positive predictive value was 78.6% (95% CI, 60.5%-89.8%) and estimated negative predictive value was 75.0% (95% CI, 55.1%-88.0%) (**Figure 4**).

Discussion

Our results indicate that regular cannabis users appear to display an increase in N95 implicit time on PERG results with no modification in N95 amplitude. Typical PERG traces are presented in the eFigure in the Supplement. This finding provides evidence for a delay of approximately 10 milliseconds in the transmission of action potentials evoked by the RGCs. As this signal is transmitted along the visual pathway via the optic nerve and lateral geniculate nucleus to the visual cortex, this anomaly might account for altered vision in regular cannabis users.

Although this anomaly found in regular cannabis users was not associated with visual symptoms, we think it may underlie several deficits in information processing. The effects of regular cannabis use on the main cognitive functions, such as memory, attention, executive function, psychomotor function, and decision making, have been the subject of many studies.[24] For example, regular cannabis use reduces the speed of information processing, leading to attentional disorders, and can cause psychomotor retardation. Retinal processing also seems to be slowed in regular cannabis users, although, paradoxically, regular users tend to respond very quickly and impulsively during several tasks to assess risk-taking and impulsivity. This alteration detected in retinal function could be an early marker of cognitive deterioration affecting high-level cognitive functions in regular cannabis users.

Limitations

This study has several limitations. First, it is a pilot study involving a small number of participants. Consequently, PERG measurements would need to be replicated in a larger population. Second, because cannabis is widely used in conjunction with tobacco, particularly mixed together in joints, it is difficult to distinguish the effect of each compound. To our knowledge, the effect of chronic administration of nicotine on PERG results has not yet been investigated. A control group of tobacco smokers could be useful for differentiating between cannabis- and tobacco-associated effects. Third, although we found a delay in the response of the RGCs, we do not know if this delay is also detected at previous retinal stages. Full-field electroretinography measurements might be useful for addressing this issue. Similarly, another PERG component, namely P50, is of particular interest for studying macular function. We would need to assess parameters extracted from this wave—amplitude and implicit time—and its morphologic features to find out more about the effect of cannabis use on retinal functioning. Finally, in future studies involving PERG measurements, it would be important to have visual acuity of at least 20/20 in each eye. All these limitations could be addressed in the future.

Here, we assume that cannabis affected the RGC response because our results are still significant when alcohol use is integrated in statistical analysis. Although alcohol and cannabis have an opposite action on glutamatergic signaling pathways,[20,25] it cannot be ruled out that an interaction between them had an effect on the RGC response. This possibility should be explored in further studies including, for example, a control group of alcohol users. Cannabis users in our study share the same pattern as in other studies; namely, they are also alcohol users and have a lower educational level.[26,27] Finally, it would be premature to interpret the sensitivity and specificity of the findings given that our study is a pilot study involving a small number of participants.

Such alterations are found in other pathologic conditions, such as various optic neuropathic disorders, and can reveal axonal injuries or apoptosis of RGCs, which are commonly detected with tests such as PERG.[28] The fact that an increase in N95 implicit time was found with no modification in N95 amplitude suggests that the total number of cells involved in the RGC response was unchanged but argues in favor of a loss of their functional properties.[29] Accordingly, in some cases, such as optic demyelinating neuropathic conditions, modifications in the N95 wave, coupled or not with alterations in the P50 wave—the first positive PERG wave representing the macular function[22]—can discriminate between the acute or chronic state of the disease and may be of prognostic value.[29] Consequently, the P50 wave should be the subject of future study.

We suggest that these anomalies may be linked to dysfunctions in retinal glutamatergic transmission given that the

effects of cannabis on glutamatergic transmission have already been demonstrated in the central nervous system.[5,20] In addition, in the vertebrate retina, glutamate is one of the main neurotransmitters involved in the vertical transmission of retinal information[18,19] and is released by the RGCs.[30] We hypothesize that, as a result of exocannabinoids, such as tetrahydrocannabinol acting on retinal endocannabinoids, regular cannabis use may modulate the retinal level of glutamate, thus altering the retinal signal elicited by the RGCs. However, other neurotransmitter-signaling pathways expressed in the retina, such as dopaminergic and gamma-aminobutyric acidergic, could be targeted by exocannabinoids. Thus, other retinal electrophysiologic measurements, such as full-field electroretinography and multifocal electroretinography, could yield critical information about the effect of regular cannabis use on retinal functioning. The precise mechanisms underlying these anomalies on PERG results need to be investigated with a view to understanding the biological underpinning of retinal functional anomalies found in cannabis users.

Conclusions

To our knowledge, this is the first study to show RGC dysfunctions in regular cannabis users. Such results are particularly relevant for exploring the cerebral effect of cannabis on synaptic transmission since retinal processing is easily measurable and not affected by high-level cognitive functions. Assessments of retinal function could therefore provide valid, reliable, and reproducible measurements that could reflect cannabis-associated brain dysfunctions. Cannabis use is widespread worldwide and, consequently, the subject of great interest in terms of public health prospects. Independent of debates about its legalization, it is necessary to gain more knowledge about the different effects of cannabis so that the public can be informed. Future studies may shed light on the potential consequences of these retinal dysfunctions for visual cortical processing and whether these dysfunctions are permanent or disappear after cannabis withdrawal.

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Author Contributions: Drs Schwitzer and Laprevote had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Schwitzer and Schwan contributed equally to this work.
Study concept and design: Schwitzer, Schwan, Albuisson, Giersch, Angioi-Duprez, Laprevote.
Acquisition, analysis, or interpretation of data: All authors.
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Invited Commentary

Retinal Ganglion Cell Dysfunction in Regular Cannabis Users
Is the Evidence Strong Enough to Consider an Association?

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Cannabis is widely used, and over the last decade, this drug has been legalized in several jurisdictions. Many others are considering this change. While public information and road safety campaigns have consistently focused on alcohol, cannabis-related toxicity has been relatively neglected as a public health issue. Further, rigorous investigation of this drug is therefore timely and appropriate.

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We read with interest the study by Schwitzer et al[1] in which the pattern electroretinogram (PERG) was used as a measure of retinal ganglion cell function. They conclude that regular use of cannabis is associated with a delay in the PERG N95 component and infer this represents delayed transmission of action potentials from the retina to the visual cortex. However, shortcomings in the study design, methods, and data analysis, acknowledged in part by the authors, weaken their conclusions.

The authors identified a study group of "regular cannabis users."[1] Perhaps because this drug is illegal, the amount and purity of drug consumed by each participant could not be determined. Dose delivery via inhalation is notoriously variable, depending on smoking dynamics.[2] Urine screens were used as proof of tetrahydrocannabinol consumption and absence of other unspecified illicit substances, but more direct measures, such as blood concentrations, were not obtained. The authors recognized but did not consider in their analyses the possible confounding influence of tobacco,[1] shown by others[3] to influence electrophysiological parameters, including the PERG, multifocal ERG, and cortical pattern visual evoked potential. Other than alcohol, the long-term exposure to other drugs, diet, and lifestyle are other variables with potential effects on retinal electrophysiology.

It is not clear why the analysis is limited to the PERG N95 component. N95 and approximately 70% of the P50 component arise in the retinal ganglion cells, but some of P50 is generated by more anterior or distal retinal structures.[4-6] Pattern ERG P50 reduction or delay usually reflects macular cone or macular cone bipolar dysfunction with concomitant alteration of N95, generated downstream from P50.[5] This can occur in the absence of visible fundus change. Pattern ERG P50 reduction may also result from severe retinal ganglion cell dysfunction, but often in association with shortening of P50 peak time. Pattern ERG P50 is also attenuated by optical factors and poor fixation. The authors acknowledge the importance of P50 assessment but do not quantify or characterize this component.[1] Pattern ERG P50 timing and amplitude may have influence on N95 parameters, and omission from this study substantially weakens the strength of the evidence of the potential association of regular cannabis use and retinal ganglion cell dysfunction.

The authors consider that averaging a large number of PERG responses ensured the reproducibility of the results.[1] While this may improve the signal-to-noise ratio of a single recording (providing participants did not become fatigued and less able to fixate and focus on the pattern stimulus), it does not demonstrate reproducibility, usually considered