Digital Biomarkers

Research Reports – Research Article

Digit Biomark 2024;8:83–92
DOI: 10.1159/000538561

Received: October 25, 2023
Accepted: March 23, 2024
Published online: April 26, 2024

A Study of Pupil Response to Light as a Digital Biomarker of Recent Cannabis Use

Suneeta Godbole[a] Andrew Leroux[a] Ashley Brooks-Russell[b]
Prem S. Subramanian[c, d] Michael J. Kosnett[e, f] Julia Wrobel[g]

[a]Department of Biostatistics and Informatics, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [b]Injury and Violence Prevention Center, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [c]Departments of Ophthalmology, Neurology, and Neurosurgery, Sue Anschutz-Rodgers Eye Center, CU School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [d]Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, MD, USA; [e]Department of Medicine, University of Colorado School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [f]Department of Environmental and Occupational Health, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [g]Department of Biostatistics and Bioinformatics, Emory University, Atlanta, GA, USA

Keywords
Pupillary light reflex · Pupillometry · Cannabis · Functional data analysis · Substance use detection

Abstract
Introduction: Given the traffic safety and occupational injury prevention implications associated with cannabis impairment, there is a need for objective and validated measures of recent cannabis use. Pupillary light response may offer an approach for detection. ***Method:*** Eighty-four participants (mean age: 32, 42% female) with daily, occasional, and no-use cannabis use histories participated in pupillary light response tests before and after smoking cannabis ad libitum or relaxing for 15 min (no use). The impact of recent cannabis consumption on trajectories of the pupillary light response was modeled using functional data analysis tools. Logistic regression models for detecting recent cannabis use were compared, and average pupil trajectories across cannabis use groups and times since light test administration were estimated. ***Results:*** Models revealed small, significant differences in pupil response to light after cannabis use comparing the occasional use group to the no-use control group, and similar statistically significant differences in pupil response patterns comparing the daily use group to the no-use comparison group. Trajectories of pupillary light response estimated using functional data analysis found that acute cannabis smoking was associated with less initial and sustained pupil constriction compared to no cannabis smoking. ***Conclusion:*** These analyses show the promise of pairing pupillary light response and functional data analysis methods to assess recent cannabis use.

Introduction

According to the National Survey on Drug Use and Health, the rates of cannabis consumption have increased in adults over 26, and adults aged 18–25, from 4.0% to

karger@karger.com
www.karger.com/dib

Correspondence to:
Suneeta Godbole, suneeta.godbole@cuanschutz.edu

14.3% and from 17.3% to 25.9% from 2002 to 2022, respectively [1]. Along with increases in consumption, there have been increases in cannabis-involved motor vehicle fatalities from 9.0% in 2000 to 21.5% in 2018 [2, 3]. Additionally, cannabis consumption at or before work is of concern to employers, especially for employees involved in safety-sensitive tasks, although there is mixed evidence on occupational injury risk [4, 5].

Current methods used to enforce existing regulations on drug-impaired driving have multiple limitations for assessing recent cannabis use. The Standardized Field Sobriety Test (SFST) is a general test for alcohol and drug impairment [6]. While shown to be an accurate and reliable assessment for alcohol impairment, it has limited ability to identify recent cannabis use [7]. In addition, many assessment tests have shown a reduction in effectiveness when administered to frequent cannabis users due to drug tolerance, leading to potential false-negative results for frequent users [8, 9]. One example is the blood metabolite, delta-9-THC which may be used to identify cannabis use; however, predictive models have better performance in participants abstaining for several days compared to those who exhibit more frequent or daily use [10]. This is due to the fact that frequent users can maintain elevated levels of blood THC for weeks after consumption; as such, frequent cannabis users may have a positive blood test for THC even if they have not recently smoked cannabis [10]. In a recent systematic review by Manning et al. [11], the authors reviewed studies of a variety of oculomotor measures used in roadside safety tests and vehicle safety systems. Some measures, such as saccadic accuracy, fixation duration, fixation rate, and visual regression, have consistent effects across studies, while others such as vertical and horizontal nystagmus are not reliably reproduced or depend on the administered test [11]. This review indicates that these measures may vary with frequency of cannabis use, and future studies should focus on a broad spectrum of consumption patterns [11]. Given the limitations of blood THC levels and existing roadside assessments, there is a need for the development of objective markers of recent cannabis use.

One potential biomarker is the pupillary light reflex test, which Drug Recognition Experts have used as an indicator of the pharmacodynamic effects of drugs and alcohol [6, 12]. This test is administered by shining a light in the eye of the participant and measuring pupil size over the course of several seconds after the onset of illumination. Figure 1 shows a typical pupillary response to light during the light reflex test, which we refer to as a *pupillary light response trajectory* throughout the paper. After the light is shined, the pupil begins to constrict in size until it reaches a minimum, called the *point of minimal constriction*, and then it begins to increase in size back toward its original diameter. The area under the curve from the point of minimal constriction to the end of the light response test is known as the *rebound dilation*.

Studies examining pupillary light response using device-recorded, light-induced, pupil constriction have shown reductions in pupil diameter after cannabis use [13–15]. However, studies of static pupil diameter produced mixed results after acute cannabis smoking or vaping, with some showing increases [16–18] and others decreases [19, 20] and some with no change [14, 21]. Recently, Steinhart et al. [15] found that acute cannabis smoking was significantly associated with diminished pupillary constriction during a light response test. The findings of Steinhart et al. [15] utilized single-number summaries of the full pupillary response such as the point of minimal constriction. Additionally, significant differences in the extent of pupillary constriction were only found after adjusting for pre-smoking values, which undermines the utility in roadside applications where baseline measurements may be unavailable. Ignoring the trajectories results in a loss of information that could potentially be utilized to better discriminate between recent and no cannabis use, regardless of cannabis use history.

The primary goal of this paper was to investigate the full pupillary light response trajectories as predictors of recent cannabis use, irrespective of pre-smoking information. We first use these pupil light response trajectories to detect recent cannabis use as compared to no use. We next examine the impact of cannabis use history on the pupil response trajectories by comparing participants with a history of no recent cannabis use, occasional cannabis use, and daily cannabis use. Finally, we estimate pupillary light response trajectories at 60, 65, and 70 min after cannabis use to explore how pupil response may change as cannabis intoxication diminishes.

Methods

Sample Information

Data are from a larger study examining effects of acute cannabis consumption among participants with occasional and daily cannabis use histories, to understand differences due to tolerance. A convenience sample of participants was recruited into one of three groups according to their history of cannabis use. Daily cannabis consumption was defined as smoking or vaping a cannabis flower product at least once per day for 30 days prior to enrollment. Occasional consumption was defined as smoking or vaping cannabis flower product on at least 1 day but no more than 2 days per

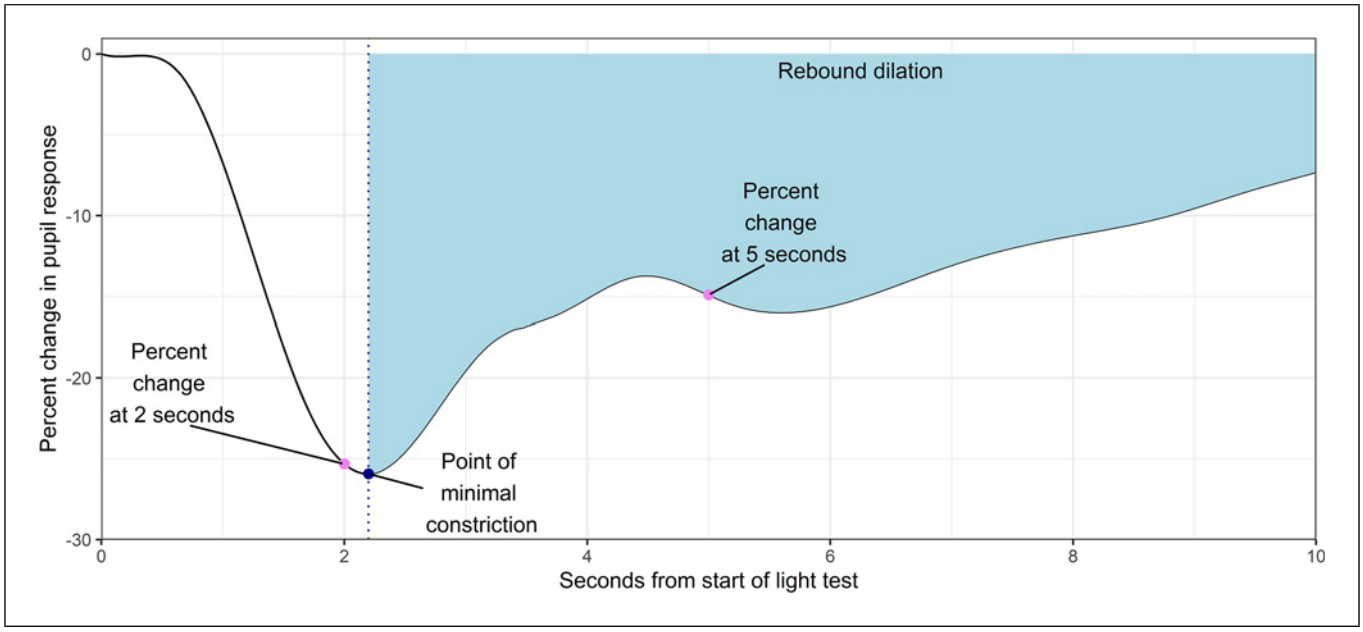

Fig. 1. A typical pupillary response to light during the light reflex test, which we refer to as a *pupillary light response trajectory* throughout the paper. At the onset of illumination (time 0 on the *x*-axis), the pupil begins to constrict in size until the diameter reaches a minimum, called the *point of minimal constriction*, and then it begins to increase in size back toward its original diameter. The area under zero on the *y*-axis from the point of minimal constriction to the end of the light response test is a measure of *rebound dilation*. The larger the magnitude of this area (i.e., larger shaded in Fig. 1), the less rebound dilation that has occurred.

week in the 30 days prior to enrollment. No cannabis consumption was defined as not having used cannabis in the month prior to enrollment. Participants were instructed not to smoke cannabis for at least 8 h and not to use edible cannabis for at least 12 h before data collection. Participants in the daily and occasional use groups were observed to smoke or vape cannabis flower during a 15-min interval and were instructed to smoke ad libitum "the amount you commonly use for the effect you most commonly desire." Participants in the no-use group were invited to relax for the equivalent amount of time. Written informed consent was obtained, and the study was approved by the Colorado Multiple Institutional Review Board, approval number 17-0075. More details on participant enrollment and screening criteria are previously published [22].

Pupil Response to Light Assessment

Videos of pupil response during the light test were collected using SafetyScreen™ infrared video goggles developed by Ocular Data Systems, Inc (Pasadena, CA, USA). Although ultimately intended to be used as a portable device that could take measurements in the field, the current research version of the device was mounted on a stand and participants sat upright with their faces positioned in contact with the device. Trajectories of pupil size during the light response test were extracted from the videos as described in Steinhart et al. [15]. These trajectories, as shown in Figure 2, represent percent change in pupil size from the start of the light test, for the right eye, after cannabis consumption, in the occasional and daily use groups, and after a short rest period for the no-use control group. Pupil light response trajectories were truncated to 400 frames, approximately 13.3 s after the start of the light test.

Functional Data Analysis

Functional data analysis (FDA) is a field of statistics that models functions (e.g., full trajectories/time series of pupillary light response) without extracting predefined specific features [23, 24]. In our analysis, a single functional unit is the pupillary light response trajectory for a single subject. This functional unit is denoted $y_i(t)$ or $x_i(t)$ for participant i, depending on whether the trajectory is modeled as the outcome or predictor, respectively, with t specifying the time at which the measurement was assessed. For example, if a participant has the pupillary light response trajectory shown in Figure 1, with pupil change of −25.3% at 2 s after the start of the light test, then $y_i(t) = y_1(2) = -25.3$. Similarly, at 5 s after the start of the light test $y_1(5) = -14.9$.

Detecting Recent Cannabis Use via Functional Logistic Regression

We use a functional logistic regression (LogRegr) model to discriminate between those who recently smoked cannabis (combining individuals with daily and occasional use patterns) and those who did not. Functional LogRegr [24–26] relates binary responses y_i (e.g., recent cannabis use vs. no use) to a functional covariate $x_i(t)$ (the pupil response trajectory for the i^{th} participant). This model is analogous to LogRegr and is given by

$$\text{logit}\left(P\left(y_i = 1\right)\right) = \beta_0 + \int_t \beta_1(t) x_i(t) \quad (1)$$

The coefficient $\beta_1(t)$ can be thought of as a weight function, with larger absolute values indicating that pupillary light response

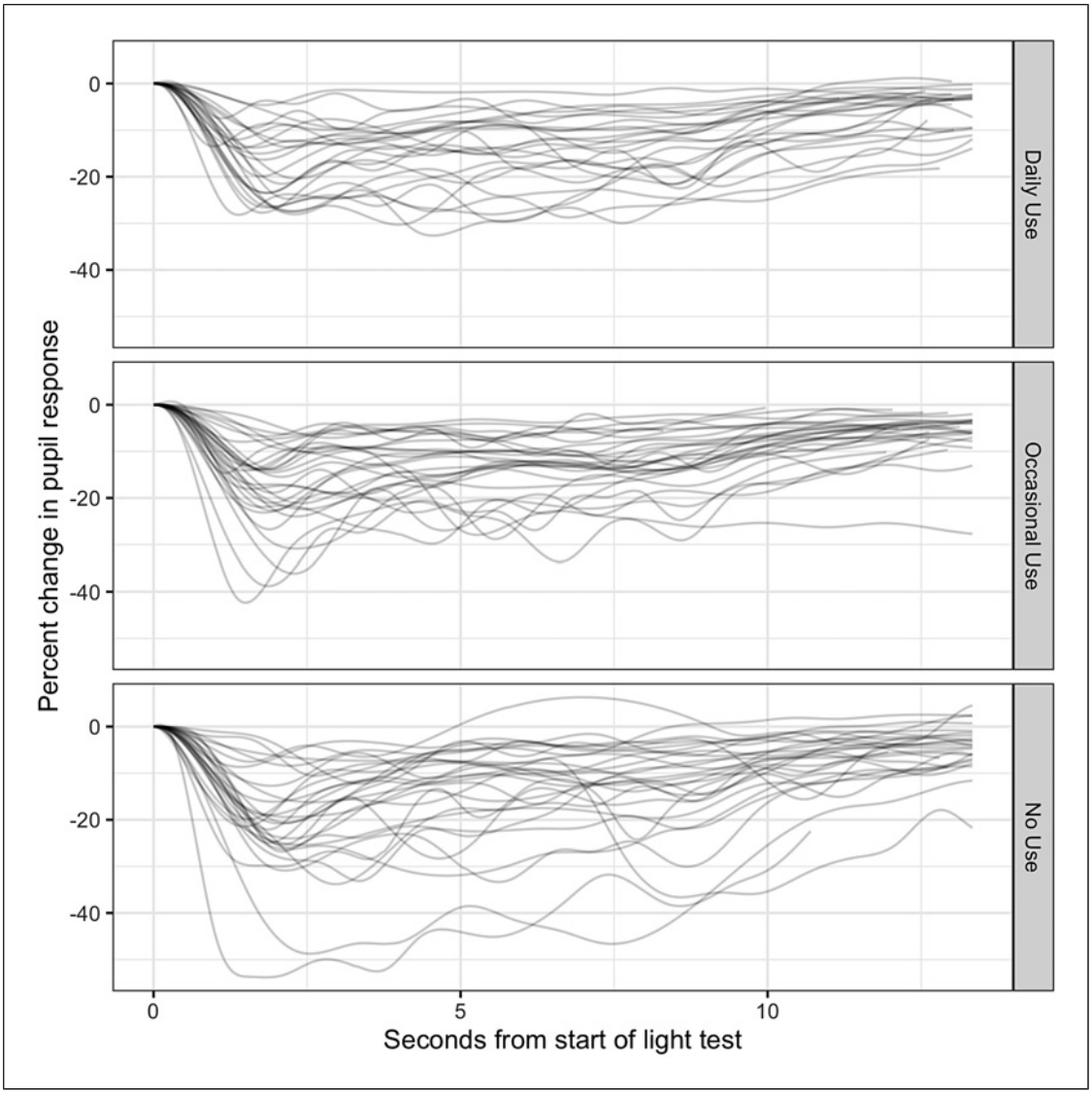

Fig. 2. The plot shows the individual participant, right eye, pupil trajectories after cannabis consumption during the pupil response to light test by cannabis use group.

is more strongly associated with the response (recent cannabis use) at a given time during the light test. When exponentiated, $\beta_1(t)$ is interpreted as an odds ratio (OR) at each time t. The integral effectively takes a weighted average of the covariate effect over the test time. This model can be used to detect recent cannabis use by leveraging the full pupillary light response trajectory.

We compare the functional LogRegr model to a traditional LogRegr model, including (a) minimal constriction; (b) rebound dilation; and (c) the slope of the rebound from the point of minimal constriction to the end of the test as calculated in [15]. For rebound dilation, a larger magnitude of area under the curve corresponds to less rebound dilation. We compare both models in their ability to detect recent cannabis use and expect better detection from the functional LogRegr model. Area under the receiver operating characteristic curve (AUC) is used to compare the ability of each model to discriminate between recent cannabis use and no use, where values closer to 1 are interpreted as having a higher discrimination accuracy. The statistical significance of differences between AUCs was calculated with a Mann-Whitney U-statistic [27].

Modeling Patterns in Pupil Response Trajectories across Cannabis Use Groups

We use function-on-scalar regression (FoSR) to model average pupil response trajectories for participants with no cannabis use, patterns of occasional cannabis use, and daily cannabis use. FoSR is analogous to linear regression and relates functional responses $y_i(t)$

to scalar covariates x_i (e.g., age, cannabis use group, gender). The FoSR model is

$$y_i(t) = \beta_0(t) + \beta_1(t)I(use\ group = occasional) + \beta_2(t)I(use\ group = daily) + \varepsilon_i(t) \quad (2)$$

Indicators of cannabis use group are denoted by *I(use group = occasional)* and *I(use group = daily)*, which take values of 1 for subjects in the specified category and 0 otherwise. Coefficients $\beta_0(t)$, $\beta_1(t)$, and $\beta_2(t)$ are akin to regression coefficients in linear regression, defined at each time t during the pupillary light response test. The intercept $\beta_0(t)$ is interpreted as the average trajectory of a participant in the no-use control group. $\beta_1(t)$ and $\beta_2(t)$ are the average differences at a specific time t between the occasional use and no-use groups, and the daily use and no-use groups, respectively. The error term $\varepsilon_i(t)$ is normally distributed and independent across participants, but the errors may be correlated over time t.

Modeling the Effect of a Time Delay from Cannabis Use to Testing Pupillary Light Response

The mean-centered time from initiation of cannabis smoking to the pupillary light response test, referred to as a time delay (TD), is included in a second FoSR model to explore how the shape of the pupil response trajectory changes over time as cannabis effects potentially become less pronounced. Cannabis use groups were combined to form one "recent use" group, which is compared with the no-use group. This model is given by

$$y_i(t) = \beta_0(t) + \beta_1(t)I(recent\ use = 1) + \beta_2(t)I(recent\ use = 1) \times TD + \varepsilon_i(t) \quad (3)$$

where $y_i(t)$, $\beta_0(t)$, and $\varepsilon_i(t)$ have the same interpretation as the previous FoSR model (Equation 2). $\beta_1(t)$ is interpreted as average difference in trajectories at a specific time t comparing recent cannabis use to no use with an average TD, and $\beta_2(t)$ is the additional average difference at a specific time t for an additional minute increase in TD.

Analysis Software

All analyses were conducted using R version 4.0.2 [28]. The R packages mgcv [29–31] and refund [32] were used to implement functional data models. Estimation of the FoSR model follows the general algorithm presented by [33]. Code and data for reproducing our analysis are publicly available on GitHub, https://github.com/sunigodbole/PupilLightReflex.git.

Results

Sample

Participants ranged in age from 25.1 to 45.3 years with an average of 32 years (SD = 5.02); had an average BMI of 25.4 kg/m^2 (SD = 4.41); and were approximately 58% male (N = 49); see online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000538561). TD between the initiation of cannabis smoking and the pupil test varied from 53 to 84 min with a mean of 62.2 min (see Fig. 3a). This time interval was caused by normal variability in the time to complete other assessments in the study or to take breaks between assessments, as described in other results from the larger study [22, 34].

Detecting Recent Cannabis Use

Figure 4a shows Receiver Operator Characteristic curves (ROCs) that compare the ability of the functional and traditional LogRegr models to discriminate between recent cannabis use and no use. The functional logistic model has a higher AUC value (AUC = 0.71, 95% CI: 0.59, 0.84) than the traditional logistic model (AUC = 0.68, 95% CI: 0.56, 0.80). This indicates that the functional LogRegr model may better differentiate recent cannabis use from no use, although the difference is not statistically significant (p = 0.6).

Figure 4b shows the OR of cannabis use from functional LogRegr. This plot shows two regions with statistically significant differences between recent cannabis use and no use. The first region, between 2.03 and 3.73 s with a maximum difference at 2.97 s (OR: 2.66, 95% CI: 1.28, 5.50), corresponds to the time period where the point of minimal constriction is typically observed and shows that individuals with less pupil constriction have higher odds of being in the cannabis use group. The second region between 5.7 and 7.3 s with a peak difference at 6.57 s (OR: 0.37, 95% CI: 0.17, 0.81) occurs during the period of rebound dilation and shows that individuals with a pupil diameter closer to that at the start of the test have lower odds of being in the cannabis use group.

Visualizing Patterns in Pupil Response Trajectories across Cannabis Use Groups

Figure 5 shows differences between the average trajectories of pupil light response in daily, occasional, and no-use groups estimated using the FoSR model in Equation (2). The solid lines in Figure 5a represent estimated mean trajectories for those who did not use cannabis (purple line), for the occasional use group (light green line), and for the daily use group (dark green line). The dashed line in Figure 5a represents the estimated mean trajectory for all those who recently smoked (daily and occasional use groups combined). The no-use group had a steeper decline in pupil size, more pupil constriction, and faster rebound dilation during the light test than the occasional or daily use groups. Estimated pupil trajectories for the occasional and daily use groups were similar, with marginally less constriction in the occasional use group.

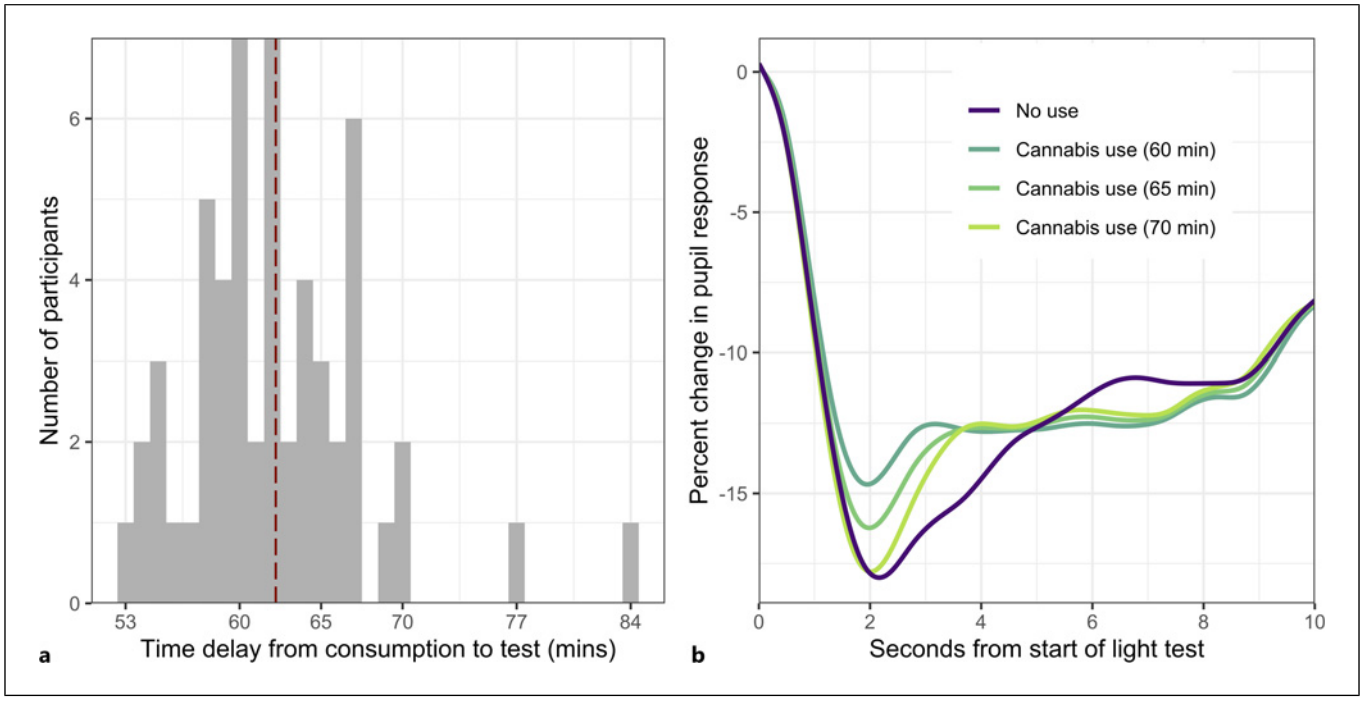

Fig. 3. a Histogram depicts the distribution of the TD from cannabis use to the pupillary light response test, in minutes. The vertical dotted red line indicates the mean of the distribution at 62.2 min. Interquartile range is 59–66 min. **b** Differences in the average pupil light response as the time from cannabis smoking increases from 60 min to 70 min (lighter color). The purple line shows the average pupil response for the no-use group. As time since cannabis consumption increases, the point of minimal constriction approaches that of the no-use group while the slope of the rebound appears to remain distinct.

Figure 5b–d shows estimates and 95% confidence intervals for the average difference in pupil response for participants in the occasional versus no-use groups, participants in the daily versus no-use groups, and participants in the daily versus occasional groups. Figure 5b, c shows regions of significant difference, indicating that there are significant differences in the average pupillary light response trajectory comparing recent cannabis use to no use, regardless of whether a participant had a history of occasional or daily cannabis consumption. Specifically, significant differences between the occasional and no-use groups are seen between 1.77 and 3.97 s with a peak difference at 2.87 s of 4.00% (95% CI: 1.32%, 6.68%), and between the daily and no-use groups between 2.1 and 2.73 s with a peak difference at 2.5 s of 2.88% (95% CI: 0.14%, 5.62%). Notably, no significant differences were found in the pupil response trajectories between the daily and occasional use groups.

The Effect of a Time Delay from Cannabis Use to Testing Pupil Light Response

Finally, we extracted expected pupil light response trajectories at 60, 65, and 70 min after cannabis use in an exploratory analysis of how pupil response changes farther out from the time of smoking. The number of minutes from cannabis smoking to administration of the pupillary light response test varied across study participants due to normal variability in the timing of study procedures, and we leverage this information to model how the pupil response trajectory is expected to change as time since cannabis smoking increases. Figure 3a shows the distribution of TD across subjects. Figure 3b depicts the average trajectory for no cannabis use, and at 60, 65, and 70 min after cannabis use.

Discussion

There are several potential applications of an objective and noninvasive digital biomarker that could distinguish recent cannabis use with reasonable accuracy, such as forensic investigations in transportation crashes or workplace incidents. Our study explored the potential for trajectories of pupil size in response to light to distinguish recent use from no recent use, among a sample of participants with a range of cannabis use histories. In the V3 framework for digital biomarker

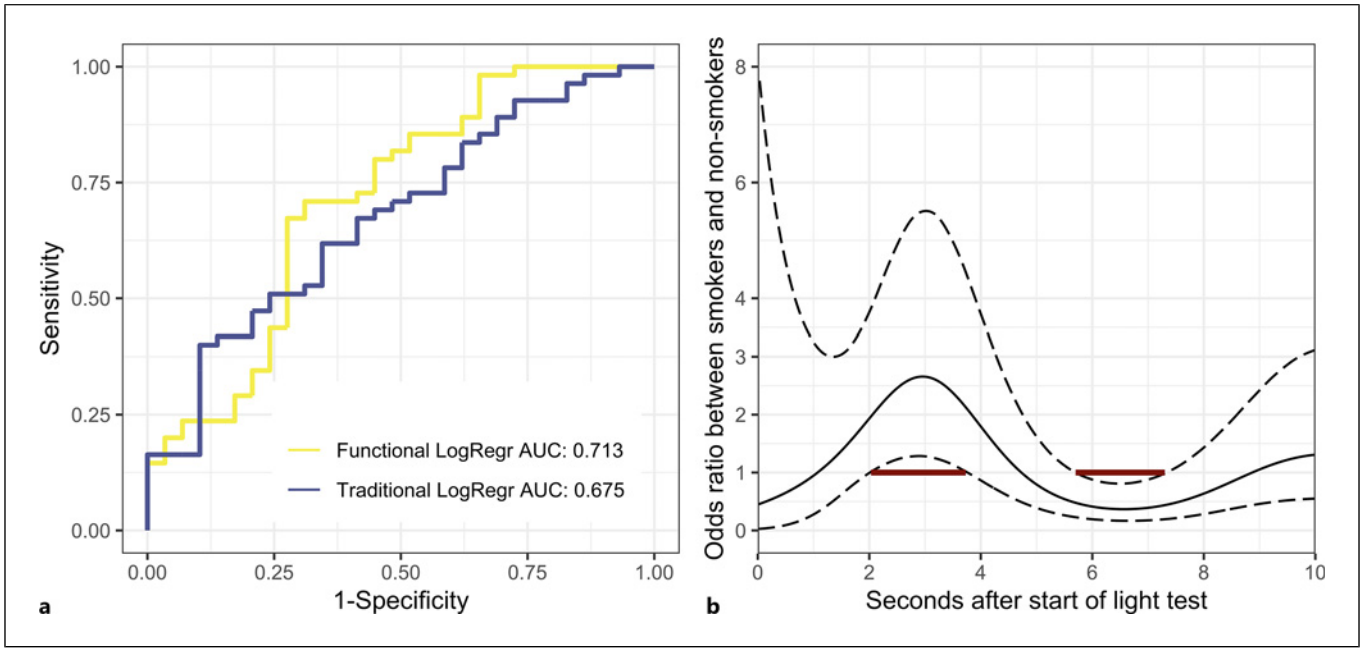

Fig. 4. a ROCs for our two LogRegr models. Higher accuracy in predicting recent cannabis use is indicated by a higher AUC and the ROC following the left and top edge of the graph. The blue line is an ROC for a traditional LogRegr model using single-value summary features of pupil light response. The yellow line is an ROC for a functional LogRegr model using full trajectory of pupil light response. The functional logistic model better differentiates between recent cannabis use and no use. **b** Solid black line depicts the OR of recent cannabis over the 10 s of the pupillary light response test. The dashed lines indicate the 95% confidence interval around the OR estimate. The red segments indicate regions where the confidence interval for the OR does not contain zero, demonstrating statistically significant differences between the recent cannabis use and no use.

development, this study provides one step in the analytic validation of pupil size response to light as a marker of recent cannabis use [35]. The current analysis suggests that pupillary light response, when paired with FDA methods that leverage information from the full pupil response trajectory, has the potential to discriminate between participants who recently smoked cannabis and those with no history of recent use without needing pre-smoking data.

Additionally, FDA methods allow interpretable visualization and statistical comparison of the average pupil responses across cannabis use groups. We found significant differences in pupil response, after cannabis smoking or an equivalent rest period, between the occasional and no-use groups for time periods that correspond to the point of minimal constriction, and less constriction was associated with higher odds of classification as a cannabis user in the discrimination model. In FoSR models, less constriction was associated with occasional and daily cannabis use when compared to the no recent use group. This difference remained significant when comparing the daily use and no-use controls. These differences may be due to more dynamic pupil movements in nonusers compared to cannabis users. Additionally, there was no significant difference when comparing the daily use and occasional use groups, indicating that tolerance effects associated with daily use may not have a significant impact on pupillary light response in our data. Taken together, this provides promising evidence that the pupillary light response trajectory may be a measure of recent cannabis use that has utility in individuals with different cannabis use histories. We were also able to model and visualize how pupil response trajectories change as time since cannabis smoking increases. As expected, the pupil response trajectories for the cannabis smoking group appear to approximate the average trajectory of the no-use group as the time since smoking increases, especially in the region of the point of minimal constriction; however, the slope of rebound dilation appears to remain distinct. The results were consistent with the hypotheses of differences in pupil light response by recent cannabis use, including frequent

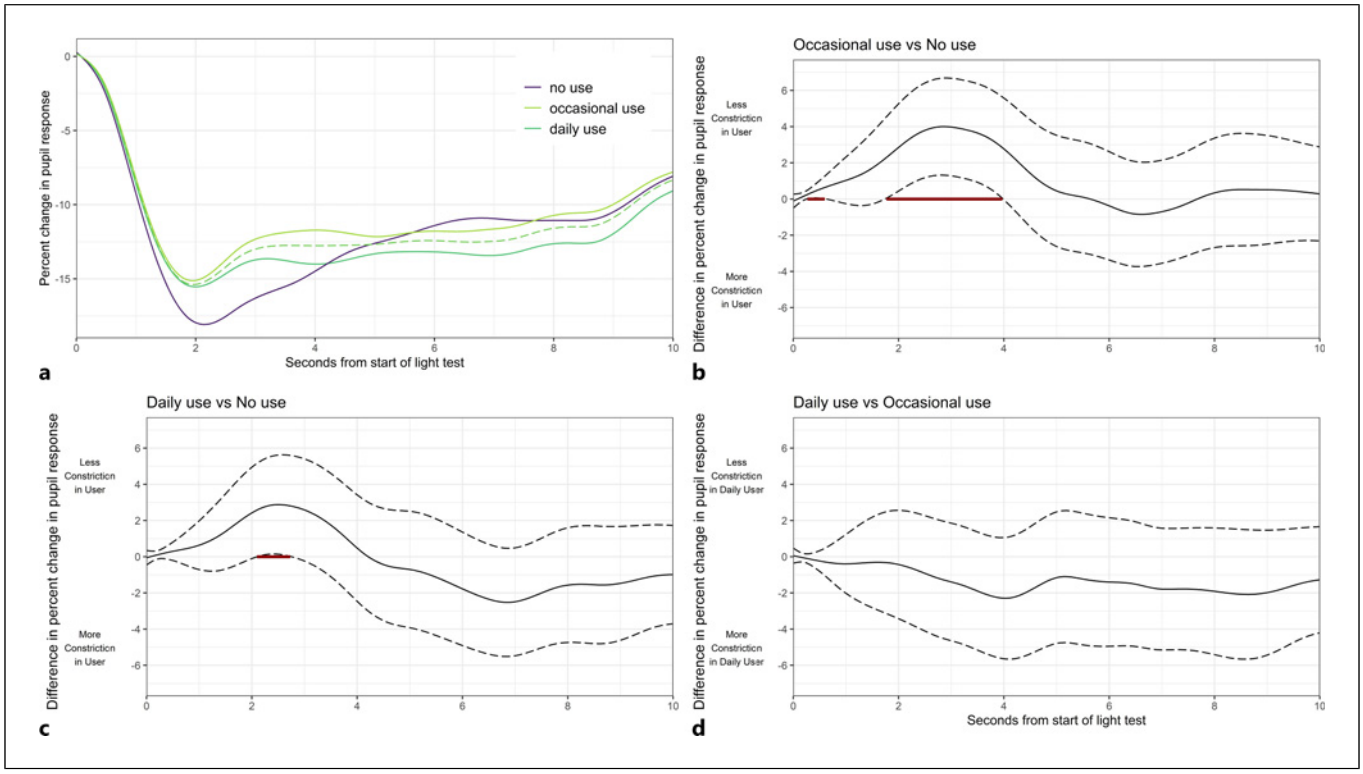

Fig. 5. a Average pupil light response trajectories plotted by cannabis use frequency. An additional dotted lined based on the average trajectory for all recent cannabis users, occasional and daily, was included to show differences between recent use and no-use groups. **b–d** Difference in average trajectories between pairs of occasional, daily, and no use of cannabis. Zero on the *y*-axis corresponds to no difference between the average trajectory of two groups, while the region indicated by the solid red line, where the confidence interval (both dashed lines) is above or below zero on the *y*-axis, indicates statistically significant differences between trajectories. The figure demonstrates significant regions of difference between occasional and no-use groups and daily and no-use groups, while there is no significant difference between occasional and daily cannabis use groups.

cannabis users, and a return to an average nonuser trajectory with delayed test time.

There are several limitations to this analysis for which more sophisticated instrumentation and future data collection will be needed. For one, the non-standardized intersubject geometry (pupil-to-camera distance) that characterized use of our specific infrared videography instrumentation rendered it possible to assess change in pupillary diameter only as a percentage difference from baseline and not in absolute size (mm). Baseline pupil diameter (in mm), which could not be measured in the present study, may be an independent predictor of the pupillary light response [36, 37]. Additionally, the start of the light test was not clearly marked in the video from the device and our team went through a manual process to define the start of the test for each participant. Although conceptualized as portable, the device's form in our study was not hand-held, which may limit utility and requires technical refinements for some settings. Future research could consider additional devices with a higher signal-to-noise ratio and clearly delineated starts and ends. In addition, it would have been valuable to examine the pupillary light response closer in time to smoking, and at a longer time interval following use to examine how the response changes over time. Other metrics of oculomotor deficits, such as saccadic accuracy and eyelid tremors, showed consistent evidence of acute cannabis use [11]; however, these metrics were not available for analysis in this study. Under these constraints, the utility of the derived model to discriminate recent cannabis use from no use assessed by AUC of the ROC plot yielded a value of approximately 0.7 (Fig. 4a). This AUC is just at the threshold for models or tests considered to have acceptable accuracy or diagnostic utility [38, 39]. Despite these limitations, the present results are promising for future research into refined measurements of pupillary changes associated with recent cannabis use.

This analysis is the first foray into pairing FDA with pupillary light response trajectories to better understand the utility of these methods in detecting recent cannabis use. We are cautiously optimistic that these results suggest that, with further refinements, quantitative measurement and analysis of pupillary light response trajectory may aid the objective assessment of recent cannabis use when only post-cannabis use measurements can be obtained.

Statement of Ethics

The study was approved by the Colorado Multiple Institutional Review Board, approval number 17-0075, and written informed consent was obtained from each participant.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This work was supported by the Colorado Department of Public Health and Environment and the National Institutes of Health (R01DA049800). The funders had no role in the design, data collection, data analysis, and reporting of this study.

Author Contributions

S.G. conducted data analysis and manuscript writing. A.B.R., J.W., M.J.K., and P.S.S. participated in the study design and implementation, and manuscript writing and editing. J.W. and A.L. created the data analysis plan and supervised analysis. A.L. also contributed to the manuscript editing.

Data Availability Statement

Data and analysis script are provided on GitHub https://github.com/sunigodbole/PupilLightReflex.git. Further inquiries can be directed to the corresponding author.

References

1 Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: results from the 2022 National Survey on drug use and Health. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; 2023.

2 Lira MC, Heeren TC, Buczek M, Blanchette JG, Smart R, Pacula RL, et al. Trends in cannabis involvement and risk of alcohol involvement in motor vehicle crash fatalities in the United States, 2000–2018. Am J Public Health. 2021;111(11):1976–85. doi: 10.2105/AJPH.2021.306466.

3 Myran DT, Gaudreault A, Pugliese M, Manuel DG, Tanuseputro P. Cannabis-involved traffic injury emergency department visits after cannabis legalization and commercialization. JAMA Netw Open. 2023;6(9):e2331551. doi: 10.1001/jamanetworkopen.2023.31551.

4 Biasutti WR, Leffers KSH, Callaghan RC. Systematic review of cannabis use and risk of occupational injury. Subst Use Misuse. 2020; 55(11):1733–45. doi: 10.1080/10826084.2020.1759643.

5 Zhang JC, Carnide N, Holness L, Cram P. Cannabis use and work-related injuries: a cross-sectional analysis. Occup Med. 2020; 70(8):570–7. doi: 10.1093/occmed/kqaa175.

6 Drug evaluation and classification (preliminary school): participant manual. National Highway Traffic Safety Administration; 2015.

7 Downey LA, King R, Papafotiou K, Swann P, Ogden E, Boorman M, et al. Detecting impairment associated with cannabis with and without alcohol on the standardized field sobriety tests. Psychopharmacology. 2012; 224(4):581–9. doi: 10.1007/s00213-012-2787-9.

8 Arkell TR, Spindle TR, Kevin RC, Vandrey R, McGregor IS. The failings of *per se* limits to detect cannabis-induced driving impairment: results from a simulated driving study. Traffic Inj Prev. 2021;22(2):102–7. doi: 10.1080/15389588.2020.1851685.

9 Wurz GT, DeGregorio MW. Indeterminacy of cannabis impairment and Δ9-tetrahydrocannabinol (Δ9-THC) levels in blood and breath. Sci Rep. 2022;12(1):8323. doi: 10.1038/s41598-022-11481-5.

10 Burt TS, Brown TL, Milavetz G, McGehee DV. Mechanisms of cannabis impairment: implications for modeling driving performance. Forensic Sci Int. 2021;328:110902. doi: 10.1016/j.forsciint.2021.110902.

11 Manning B, Downey LA, Narayan A, Hayley AC. A systematic review of oculomotor deficits associated with acute and chronic cannabis use. Addict Biol. 2024;29(1):e13359. doi: 10.1111/adb.13359.

12 Richman JE, McAndrew KG, Decker D, Mullaney SC. An evaluation of pupil size standards used by police officers for detecting drug impairment. Optometry. 2004; 75(3):175–82. doi: 10.1016/S1529-1839(04)70037-8.

13 Campobasso CP, De Micco F, Corbi G, Keller T, Hartung B, Daldrup T, et al. Pupillary effects in habitual cannabis consumers quantified with pupillography. Forensic Sci Int. 2020;317:110559. doi: 10.1016/j.forsciint.2020.110559.

14 Fant R, Heishman SJ, Bunker EB, Pickworth WB. Acute and residual effects of marijuana in humans. Pharmacol Biochem Behav. 1998; 60(4):777–84. doi: 10.1016/S0091-3057(97)00386-9.

15 Steinhart B, Brooks-Russell A, Kosnett M, Subramanian P, Wrobel J. A video segmentation pipeline for assessing changes in pupil response to light after cannabis consumption. bioRxiv. 2023:2023.03.17.533144. https://doi.org/10.1101/2023.03.17.533144.

16 Stark MM, Englehart K, Sexton BF, Tunbridge R, Jackson P. Use of a pupillometer to assess change in pupillary size post-cannabis. J Clin Forensic Med. 2003;10(1):9–11. doi: 10.1016/S1353-1131(02)00162-1.

17 Merzouki A, Mesa JM, Louktibi A, Kadiri M, Urbano GV. Assessing changes in pupillary size in Rifian smokers of kif (Cannabis sativa L.) q. J Forensic Leg Med. 2008.

18 Shahidi Zandi A, Comeau FJE, Mann RE, Di Ciano P, Arslan EP, Murphy T, et al. Preliminary eye-tracking data as a nonintrusive marker for blood Δ-9-tetrahydrocannabinol concentration and drugged driving. Cannabis Cannabinoid Res. 2021;6:537–47. doi: 10.1089/can.2020.0141.

19 Brown B, Adams AJ, Haegerstrom-Portnoy G, Jones RT, Flom MC. Pupil size after use of marijuana and alcohol. Am J Ophthalmol. 1977;83(3):350–4. doi: 10.1016/0002-9394(77)90732-2.

20 Ortiz-Peregrina S, Ortiz C, Castro-Torres JJ, Jiménez JR, Anera RG. Effects of smoking cannabis on visual function and driving performance. A driving-simulator based study. IJERPH. 2020;17(23):9033. doi: 10.3390/ijerph17239033.
21 Newmeyer MN, Swortwood MJ, Taylor ME, Abulseoud OA, Woodward TH, Huestis MA. Evaluation of divided attention psychophysical task performance and effects on pupil sizes following smoked, vaporized and oral cannabis administration: performance on psychophysical tasks after inhaled and oral cannabis. J Appl Toxicol. 2017;37(8):922–32. doi: 10.1002/jat.3440.
22 Brooks-Russell A, Brown T, Friedman K, Wrobel J, Schwarz J, Dooley G, et al. Simulated driving performance among daily and occasional cannabis users. Accid Anal Prev. 2021;160:106326. doi: 10.1016/j.aap.2021.106326.
23 Ramsay JO, Silverman BW. Functional data analysis. 2nd ed. New York, USA: Springer; 2005.
24 Goldsmith J, Bobb J, Crainiceanu CM, Caffo B, Reich D. Penalized functional regression. J Comput Graph Stat. 2011;20(4):830–51. doi: 10.1198/jcgs.2010.10007.
25 Ramsay JO, Dalzell CJ. Some tools for functional data analysis. J Roy Stat Soc B. 1991;53(3):539–61. doi: 10.1111/j.2517-6161.1991.tb01844.x.
26 Reiss PT, Goldsmith J, Shang HL, Ogden RT. Methods for scalar-on-function regression. Int Stat Rev. 2017;85(2):228–49. doi: 10.1111/insr.12163.
27 DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44(3):837–45. doi: 10.2307/2531595.
28 R Core Team. R: a language and environment for statistical computing; 2023.
29 Wood SN. Generalized additive models: an introduction with R. 2nd ed. Chapman and Hall/CRC; 2017.
30 Wood SN. Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. J Roy Stat Soc B Stat Methodol. 2011;73(1):3–36. doi: 10.1111/j.1467-9868.2010.00749.x.
31 Wood SN. Stable and efficient multiple smoothing parameter estimation for generalized additive models. J Am Stat Assoc. 2004;99(467):673–86. doi: 10.1198/016214504000000980.
32 Goldsmith J, Scheipl F, Huang L, Wrobel J, Di C, Gellar J, et al. Refund: regression with functional data; n.d.
33 Leroux A, Xiao L, Crainiceanu C, Checkley W. Dynamic prediction in functional concurrent regression with an application to child growth. Stat Med. 2018;37(8):1376–88. doi: 10.1002/sim.7582.
34 Smith SJ, Wrobel J, Brooks-Russell A, Kosnett MJ, Sammel MD. A latent variable analysis of psychomotor and neurocognitive performance after acute cannabis smoking. Cannabis. 2023;6(2):123–32. doi: 10.26828/cannabis/2023/000156.
35 Goldsack JC, Coravos A, Bakker JP, Bent B, Dowling AV, Fitzer-Attas C, et al. Verification, analytical validation, and clinical validation (V3): the foundation of determining fit-for-purpose for Biometric Monitoring Technologies (BioMeTs). NPJ Digit Med. 2020;3:55. doi: 10.1038/s41746-020-0260-4.
36 Larson MD, Behrends M. Portable infrared pupillometry: a review. Anesth Analg. 2015;120(6):1242–53. doi: 10.1213/ANE.0000000000000314.
37 McKay RE, Larson MD. Detection of opioid effect with pupillometry. Auton Neurosci. 2021;235:102869. doi: 10.1016/j.autneu.2021.102869.
38 Mandrekar JN. Receiver operating characteristic curve in diagnostic test assessment. J Thorac Oncol. 2010;5(9):1315–6. doi: 10.1097/JTO.0b013e3181ec173d.
39 Meurer WJ, Tolles J. Logistic regression diagnostics understanding HowWell a model predicts outcomes. JAMA. 2017;317(10):1068–9. doi: 10.1001/jama.2016.20441.