TITLE: Detecting changes in pupil response to light associated with cannabis consumption

Authors: Suneeta Godbole, MS

Andrew Leroux, PhD

Ashley Brooks-Russell, PhD

Prem S. Subramanian, MD, PhD

Michael J. Kosnett, MD, MPH

Julia Wrobel, PhD

ABSTRACT:

Given the public health implications of recent cannabis use for roadside safety and occupational injury prevention, there is value in objective and validated measures of recent cannabis use that may be applied to enforce regulations and reduce the risk of injury. Identifying a reliable, objective biomarker of recent cannabis use has proven challenging, but pupillary response to light may offer an avenue for detection that outperforms typical sobriety tests and blood THC concentrations. We used tools from functional data analysis to model the impact of recent cannabis smoking on trajectories of the pupillary light reflex over several seconds in participants with occasional (1 to 2 times/week) and daily cannabis use. Functional data analysis models revealed significant differences in pupil responses to light after cannabis use with statistically significant differences between 1.77 to 3.97 seconds in the average pupil response pattern between the occasional use group and a no use control group and similar differences in pupil response patterns from 2.1 to 2.7 seconds between the daily use group and no use control. Additionally, a model predicting recent cannabis use, using functional data analysis methods, outperformed a predictive model using traditional methods (AUC: 0.71 vs 0.68). These analyses show the promise of pairing pupil 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 7.9% and from 17.3% to 22.1% from 2002 to 2017, 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]. Additionally, cannabis consumption at or before work is of concern to employers with regards to risk of occupational injury; however, the research on this association is mixed [3, 4] with temporality of exposure being a major limitation of the extant literature. An objective, easy to obtain biomarker of recent cannabis use may be of value in field assessments, particularly in the context of investigation of motor vehicle crashes and occupational mishaps.

To enforce existing regulations on drug impaired driving, we need non-invasive, portable, and objective assessment of recent drug use. The Standardized Field Sobriety Test is a general test for alcohol and drug impairment, comprised of the horizontal gaze nystagmus, walk and turn and one-leg stands [5]. While shown to be an accurate and reliable assessment for alcohol impairment, it has limited ability to identify cannabis use [6]. In addition, many of these tests have shown a reduction in effectiveness when administered on frequent cannabis users due to drug tolerance effects, leading to potential false negatives for frequent users. Many states and countries reference drug levels in the blood as a threshold for impaired, modeled on the .08% blood alcohol level used as a *per se* definition of alcohol impairment. The parallel would be the blood level of delta-9-THC; however predictive models have better performance in participants abstaining for several days compared to those who exhibit more frequent or daily use [7]. This is in part due to the fact that frequent users can maintain elevated levels of blood THC for days or weeks after consumption; as such, frequent cannabis users may have a blood test positive for THC even if they have not recently smoked cannabis [7]. 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 and impairment from cannabis use.

Drug Recognition Experts, specially trained law enforcement officers, have included pupillary and ocular signs as indicators of the pharmacodynamic effects of drugs and alcohol [8, 9]. They may examine pupil size under illumination ranging from near total darkness to bright light and assess the pupillary light reflex, which consists of constriction in response to visible light. This is similar to the pupillary light response test that is performed clinically to assess central nervous system function and acute drug effects. 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 light is turned off. Studies of the pupillary light reflex in cannabis users have yielded inconsistent results [10, 11]. Moreover, detailed assessment of the entire pupillary light response trajectory following acute cannabis consumption is lacking. If the pattern of pupillary response to light were found to be indicative of recent cannabis use, or impairment from cannabis use, especially in the context of habitual use, its use as a biomarker could contribute to the assessment of impaired driving or have utility in investigations of cannabis use in the workplace and other controlled settings.

Recently, Steinhart et al [12] found evidence that acute cannabis smoking is significantly associated with diminished pupillary constriction during a light response test conducted using visible light and pupillary recording by infrared videography. Both occasional and daily cannabis users displayed this response, to a similar extent, compared to non-using control subjects. However, the finding of Steinhart et al, utilized single number summaries, such as point of minimal constriction, extracted from the full pupillary response trajectories depicted in Figure 1 as a basis for the between group comparisons. Ignoring these trajectories results in a loss of information that could potentially be utilized to better discriminate between cannabis use groups [12]. Additionally, significant differences in the point of minimal constriction were found after adjusting for pre-smoking values, which undermines the utility in field applications.

The primary goal of this paper is to investigate the full pupillary light response trajectories collected in the study conducted by Steinhart et al [12] as predictors of recent cannabis use, irrespective of pre-smoking pupil diameter. Our analysis uses tools from a field of statistics known as functional data analysis (FDA). The main conceptual underpinning of FDA is to model the whole pupil light response trajectory as a unit of observation, leveraging information contained in the temporal structure of the data and estimating time-specific effects. This approach utilizes maximal information which is lost when only considering single number predictors such as point of minimal constriction and rebound dilation [13, 14]. In this analysis, we will use FDA modeling techniques to accomplish the following objectives. We first use the full pupil response trajectories to predict 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 no cannabis use, occasional cannabis use, and daily cannabis use. Finally, we extract expected pupillary light response trajectories at 60, 65, and 70 minutes after cannabis use to explore how pupil response may change over time.

METHODS:

*Sample Information:*

Data are part of a larger study examining effects of acute cannabis consumption on simulated driving among participants with occasional and daily cannabis use histories. Daily cannabis consumption was defined as smoking or vaping a cannabis flower product at least one time per day, every day of the week for 30 days prior to enrollment; occasional consumption was defined as smoking or vaping cannabis flower product on at least one day but no more than two days per week in the 30 days prior to enrollment; and no cannabis consumption was defined as not having used cannabis in the month prior to enrollment. Participants in the daily and occasional use groups were observed to smoke or vape cannabis flower during a 15-minute 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. More details on participant enrollment and screening criteria are previously published [15].

In the sample of 84 participants used in this analysis, there were 29 participants in the no-use group, and 30 and 25 participants in the occasional and daily use groups, respectively. 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/m2 (sd = 4.41); and were approximately 58% male (N = 49); see Table 1. THC levels were assessed from whole blood collected 30 minutes after the inception of a 15-minute *ad-libitum* smoking interval. Time between cannabis smoking and the pupillary light response test varied from 53 – 84 minutes with a mean of 62.2 minutes (see Figure 4A). This time interval reflects the time used to complete other assessments such as a driving simulator test, as described in the study protocol.

Table 1:

|  | **Cannabis Use Group** | | |  | |
| --- | --- | --- | --- | --- | --- |
| **Characteristic** | **non-user** (N = 29)1 | **occasional** (N = 30)1 | **daily** (N = 25)1 | **Total** (N = 84)1 | **p-value**2 |
| **Age (years)** | 32.29 (4.70) | 31.15 (4.75) | 32.75 (5.71) | 32.02 (5.02) | 0.5 |
| **Sex** |  |  |  |  | 0.2 |
| Female | 16 (55%) | 10 (33%) | 9 (36%) | 35 (42%) |  |
| Male | 13 (45%) | 20 (67%) | 16 (64%) | 49 (58%) |  |
| **Body Mass Index (kg/m2)** | 24.94 (4.72) | 24.49 (3.96) | 27.08 (4.26) | 25.42 (4.41) | 0.066 |
| **THC, after cannabis smoking (ng/ml)** | 0.0 (0.0, 0.0) | 5.73 (3.73, 9.47) | 17.84 (8.20, 42.42) | 3.96 (0.0, 13.60) | NA |
| **Time Interval of pupillary measurements after initiation of cannabis smoking (mins)** | NA | 63.93 (6.26) | 60.16 (3.78) | NA |  |
| 1Mean (SD); n (%); Median (IQR) | | | | | |
| 2Kruskal-Wallis rank sum test; Pearson's Chi-squared test | | | | | |

*Pupil Response to Light Reflex Assessment*:

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*, then it begins to increase in size back towards 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*.

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| Figure 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*, then it begins to increase in size back towards 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*. |

Videos of pupil response during the light test were collected using SafetyScanTM infrared videography goggles developed by Ocular Data Systems, LLC. Trajectories of pupil size during the light response test, like that shown in Figure 1, were extracted from the videos using the video segmentation pipeline described in Steinhart et al [12]. These trajectories 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 seconds 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 pre-defined specific features [14]. These functions may be either the outcome (the whole trajectory is the outcome) or a predictor, or both. The methods are designed to handle complicated (e.g. highly non-linear) data and associations, while accounting for within person correlations over the function. For example, in the current context, FDA methods allow for estimating and quantifying uncertainty for differences in patterns of pupillary light response vary over time by cannabis use history. In our analysis, a single functional unit is the pupillary light response trajectory for a single subject. This functional unit is denoted or for participant *i*, depending on whether the trajectory is modelled 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 seconds after the start of the light test, then . Similarly, at 5 seconds after the start of the light test .

Our analysis uses two distinct FDA methods to model differences in pupil response to light after cannabis use. The first method, functional logistic regression (aka scalar-on-function regression), is used to predict whether or not a subject recently used cannabis and treats the pupil response trajectory as a predictor variable. The second method, function-on-scalar regression, is used to model and visualize how patterns in the pupil response trajectories differ for participants with patterns of daily cannabis use, occasional cannabis use, and no use, and treats the pupillary light response trajectory as the outcome. These methods and their roles in this analysis are described in more detail below.

*Predicting recent cannabis use via functional logistic regression*

Here we use a functional logistic regression model to discriminate between those who recently smoked cannabis (designated “recent cannabis use”, combining individuals with daily and occasional use patterns) and those who did not (designated “no use”). Functional logistic regression [16-18] relates binary responses (e.g. recent cannabis use vs. no use) to functional covariates (the pupil response trajectory for the *ith* participant). This model is analogous to logistic regression and is given by

(1)

The coefficient can be thought of as a weight function, with larger absolute values indicating that pupillary light response (the functional covariate ) is more strongly associated with the response (recent cannabis use) at a given time. As with traditional logistic regression, the coefficient is interpreted as a log odds ratio of recent cannabis use associated with a 1% increase in pupil diameter; however, unlike traditional logistic regression, this log odds ratio is estimated at each time during the pupil light response test. When exponentiated, is interpreted as an odds ratio at each time . The integral effectively takes a weighted average of the covariate effect over the test time. This model can be used to predict recent cannabis use using the full pupillary light response trajectory.

We compare the functional logistic regression model to a traditional logistic regression model that uses single value summaries of the trajectory data, including (a) minimal constriction, the magnitude of peak decrease in pupil diameter as a percentage of the pre-illumination diameter; (b) rebound dilation, the magnitude of rebound dilation after the point of minimal constriction; and (c) the slope of the rebound after the point of minimal constriction as calculated in [12]. We compare both models in their ability to predict recent cannabis use and expect better prediction from the functional logistic regression model because it leverages information from the full pupillary light response trajectories. 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 predictive accuracy. The statistical significance of differences between AUC curves was calculated with Mann-Whitney U-statistic as described in [19].

*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 patterns of daily cannabis use. FoSR is analogous to linear regression and relates functional responses to scalar covariates (e.g. age, cannabis use group, gender). In this analysis, we chose not to use demographic characteristics in our modelling because in field cannabis testing scenarios demographic information may not be known. The FoSR model is

(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 , , and are akin to regression coefficients in linear regression, with the added advantage that they are defined at each time during the pupillary light response test. The intercept is interpreted as the average trajectory of a participant in the no use control group. is the average difference at a specific time *t* between the occasional use and no use groups, and is the average difference between the daily use and no use groups. The error term , like in traditional linear regression, is normally distributed and independent across participants, but unlike traditional linear regression, the errors may be correlated over time *t*.

*Modeling the effect of a time delay from cannabis use to testing pupillary light response*

The time from cannabis use to the pupillary light response test ranged from 53 – 84 minutes (Figure 4A). We refer to this as the time delay (TD) and include it in a second FoSR model to explore the shape of the pupil response trajectory changes as cannabis effects become less acute. Cannabis use groups were combined to form one “recent use” group, which is compared with the no use group, and the time delay (TD) from cannabis use to testing was mean centered. This model is given by

(3)

where , , and have the same interpretation as the previous FoSR model (Equation 2).

is interpreted as average difference in trajectories at a specific time *t* comparing recent cannabis use to no use with an average time delay from cannabis use to testing, and is the average difference at a specific time *t* for an additional minute increase in time since smoking for the cannabis use group.

*Analysis Software*

All analyses were conducted using R version 4.0.2 [20]. The R packages mgcv [21, 22] and refund [17] were used to implement functional data models. Estimation of the FoSR regression model follows the general algorithm presented by [23]. Code for reproducing our analysis is publicly available on GitHub.

RESULTS:

*Predicting recent cannabis use*

Figure 2A shows ROC curves that compare the ability of the functional and traditional logistic regression models to discriminate between recent cannabis use and no use. The functional logistic model, which uses the full pupillary light response trajectory, has a higher AUC value (AUC = 0.71) than the traditional logistic model based on single value summary features (AUC = 0.68). This indicates that the functional logistic regression model can better differentiate recent cannabis use from no use.

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| Figure 2: *Panel A*: Receiver Operator Characteristic curves (ROCs) for our two logistic regression (LogRegr) models. Higher accuracy in predicting recent cannabis use is indicated by a higher AUC and the ROC curve following the left and top edge of the graph. The blue line is an ROC curve for a traditional logistic regression model using single value summary features of pupil light response. The yellow line is an ROC curve for a functional logistic regression model using full trajectory of pupil light response. The functional logistic model better differentiates between recent cannabis use and no use. *Panel B*: Solid black line depicts the odds ratio (OR) of recent cannabis over the 10 seconds 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. |

An added benefit of the functional logistic regression model is the ability to visualize the odds of cannabis use over the 10 seconds of the pupil light response test (Figure 2B). 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 seconds with a maximum difference at 2.97 seconds (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 seconds with a peak difference at 6.57 seconds (OR: 0.37, 95% CI: [0.17, 0.81]), occurs during the period of rebound dilation and shows that higher values of rebound dilation, indicating more rebound dilation, decrease the odds of being in the cannabis use group.

*Visualizing patterns in pupil response trajectories across cannabis use group*

Figure 3 shows differences between the average trajectories of pupil light response in daily, occasional and no-use groups estimated using the function-on-scalar regression (FoSR) model in Equation (2). The solid lines in Figure 3A represent estimated mean trajectories for those who did not use cannabis (purple line), for those in the occasional use group who recently smoked (light green line), and for those in the daily use group who recently smoked (dark green line). The dashed line in Figure 3A 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 higher 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.

Figure 3 panels B, C, and D show estimates and 95% confidence intervals for the average difference in pupil response for participants in the occasional vs no use groups, participants in the daily vs. no use groups, and participants in the daily vs. occasional groups. Both Figure 3B and Figure 3C show regions of significant difference, indicating that there are significant differences in the average pupillary 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 to 3.97 seconds with a peak difference at 2.87 seconds of 4.00% (95% CI: 1.32%, 6.68%), and between the daily and no-use groups between 2.1 to 2.73 seconds with a peak difference at 2.5 seconds 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, indicating that tolerance effects due to daily use do not have a significant impact on pupillary light response in our data.

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| Figure 3 A-D: Panel A shows 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. Panel B shows the difference in average trajectories between pairs of occasional, daily and no-use of cannabis. The red line indicates no difference between the average trajectory of two groups, while a region where the confidence interval (both dashed lines) is above or below the red line 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. |

*The effect of a time delay from cannabis use to testing pupil light response*

Finally, we extract expected pupil light response trajectories at 60, 65, and 70 minutes after cannabis use to explore how pupil response changes. The number of minutes from cannabis smoking to administration of the pupillary light response test varied across study participants, and we leverage this information to model how the pupil response trajectory is expected to change as time since cannabis smoking decreases. Figure 4A shows the distribution of this time delay across subjects, which ranged from 53 to 84 minutes with a mean of 62.22 minutes (sd = 5.57). Figure 4B depicts the average trajectory for no cannabis use, and at 60, 65, and 70 minutes after cannabis use. Although the differences were not statistically significant, it appears as though the point of minimal constriction approaches that of the no use group while the slope of the rebound dilation as time since cannabis consumption increases.

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| Figure 4: *Panel A*: Histogram depicts the distribution of the time delay 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 minutes. Interquartile range is 59 – 66 minutes. *Panel B*: Differences in the average pupil light response as the time from cannabis use increases from 60 minutes to 70 minutes (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. |

DISCUSSION:

Forensic investigation of the potential role of recent cannabis use in transportation crashes or workplace mishaps would be aided by availability of a noninvasive measure that could assess recent use with reasonable accuracy. The current analysis suggests that pupillary light response, when paired with functional data analysis 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 on pupillary light response.

To show the utility of using functional data analysis methods, in predicting recent cannabis use, we compared the predictions from a functional logistic regression and traditional logistic regression model. While both models showed some predictive ability, the functional logistic regression model had a higher AUC indicating a better predictive ability of the model. This better predictive ability may stem from the information that is retained when modelling full pupil trajectories versus the information loss that occurs when aggregating information into single summary values used in the traditional logistic regression framework. Additionally, the functional logistic regression was plotted to depict where and how the patterns of recent use and no use groups differed significantly from each other. This plot showed two regions that were significantly different and corresponded to the point of minimal constriction and rebound dilation in typical pupillary light response trajectories. In the region of the point of minimal constriction, the model shows that less constriction is associated with higher odds of recently using cannabis, while in the region of rebound dilation, we see that less rebound dilation is associated with lower odds of recently using cannabis. This corresponds with previous evidence showing an effect of recent cannabis use on pupillary light response trajectories. However, the difference in predictive ability between the functional and traditional logistic regression were not statistically significantly difference, which may be due to data quality and instrumentation difficulties as discussed in the limitations section.

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. This difference remained significant when comparing the daily use and no-use controls but was not significantly different when comparing the daily use and occasional use groups. These differences may be due to more dynamic pupil movements in non-user compared to cannabis users. 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. These differences were not statistically significant, but this may be due to sample size and the fact that the study was not designed to estimate these effects. The results were consistent with an a-priori hypotheses of differences in pupil light response by recent cannabis use, including frequent cannabis users, and a return to an average non-user trajectory with delayed test time.

However, there are several limitations to this analysis for which more sophisticated instrumentation and future data collection will be needed. Of primary concern were data quality issues that persisted after data processing, imputation and smoothing from the video segmentation pipeline. While most pupil light response trajectories reflected the characteristic pattern of the pupillary light response there were a minority that were removed because there were no characteristic features of the light response. This led to a reduction in the sample size from a collection of 101 participants to usable data in 84. In addition, the nonstandardized inter-subject geometry (pupil to camera distance) that characterized use of 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 reflex expressed in percent change from baseline. However, in field assessment of recent cannabis use, pupil size may not be measured, so analysis using percent change from the test start may be more useful. Future research could 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. In light of the limitations noted, it speaks to the robustness of our analysis that significant differences were still detected.

This analysis is the first foray into pairing functional data analysis 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-use measurements can be obtained.

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