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Detecting changes in pupil response to light associated with cannabis consumption

Summary: The rate of cannabis consumption has increased with the legalization of cannabis for recreational and medical use. The implications of cannabis legalization on traffic and occupational safety are understudied, and there is a need for objective and validated measures of acute cannabis impairment that may be applied in public safety and occupational settings. 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 use tools from functional data analysis (FDA) to model the impact of recent cannabis consumption on trajectories of pupillary light in participants. The FDA models significant differences in pupil responses after cannabis use, and better predict recent cannabis use (AUC = 0.71) when compared to traditional methods (AUC=0.66). These analyses show the promise of pairing pupil light response and FDA methods to determine recent cannabis use potentially leading to better roadway and occupational safety.

Key words: cannabis use, function-on-scalar regression, scalar-on-function regression, pupillary light reflex, time series

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1. Introduction

According to the National Survey on Drug Use the rates of cannabis consumption has increased in adults over 26 and adults aged 18-25 from 4.0% to 7.9% and from 17.3% to 22.1%, respectively (Lira et al., 2021). 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 (Lira et al., 2021). Additionally, cannabis consumption at- or before- work is of concern to employers with regards to occupational injury; however, the research on this association is mixed (Biasutti et al., 2020; Zhang et al., 2020) with temporality of exposure being a major concern. In the review article by Biasutti, Leffers and Callaghan, approximately half of the reviewed studies showed a positive association between cannabis use and occupational injury while the other half showed no association, however 12 of the 16 studies were noted to have potentially assessed the occupational injury prior to cannabis use (Biasutti et al., 2020) To better understand the effect of acute cannabis use on driving and on occupational injuries an objective test of recent use is needed.

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 stand with an additional component of head movements and/or jerks added specifically to improve assessment of impairment due to drugs (Downey et al., 2012) While shown to be an accurate and reliable assessment for alcohol impairment, it has limited ability to identify drug use (Downey et al., 2012) 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. Another test possibility is a plasma concentration of THC and its metabolite THCCOOH from a blood draw; however predictive models have better performance in participants abstaining for several days compared to those who exhibit more frequent or daily use (Burt et al., 2021) This is in part due to the fact that frequent users

can maintain elevated levels of blood plasma 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 (Burt et al., 2021).

One test that may be able to detect recent cannabis use even in the presence of tolerance due to daily use is the pupil light response test. 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. Figure 1 shows a typical pupillary response to light during the light reflex test, which we refer to as a *pupil light response trajectory* throughout the paper, for a sober individual. 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*. There is evidence that there is less pupil constriction and slower rebound dilation due to recent cannabis consumption, but evidence is mixed and warrants further study (Campobasso et al., 2020; Fant et al., 1998).

[Figure 1 about here.]

Recently, Steinhart et. al. (Steinhart et al., 2023) found evidence that recent cannabis consumption is significantly associated with less pupil constriction during a light response test conducted using infrared videography goggles. This study examined pupil light response in participants with patterns of daily cannabis use, occasional cannabis use, and a no-use control group both before and after smoking. Notably, no significant differences were found between the daily and occasional use groups, indicating that the pupil light response test may pick up on physiological responses to cannabis consumption that are immutable to the tolerance effects of frequent cannabis use (Steinhart et al., 2023). However, significant effects were only detectable when accounting for each participant's pre-use baseline pupil

response, making it inappropriate for roadside assessments where baseline measurements are not available. In addition, Steinhart et al used single number summaries, such as point of minimal constriction, extracted from the full pupillary response trajectories depicted in Figure 1 collapsing these trajectories results in a loss of information that could potentially be utilized to better discriminate between cannabis use groups (Steinhart et al., 2023).

The primary goal of this paper is to leverage the full pupil light response trajectories from Steinhart et. al. (Steinhart et al., 2023), to detect recent cannabis use irrespective of pre-use pupil response. Our analysis uses tools from a statistical subfield called functional data analysis (FDA). The main conceptual underpinning of FDA is to model the whole pupil light response trajectory as a unit of observation, to use the temporal structure and ordering of the trajectory to estimate time-specific effects, and to utilize the information that is removed when only modeling single number summaries like point of minimal constriction and rebound dilation (Goldsmith et al., 2016; Ramsay and Silverman, 2005). 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 drug tolerance on the pupil response trajectories by comparing participants with no cannabis use, patterns of occasional cannabis use, and patterns of daily cannabis use. Finally, we extract expected pupil light response trajectories at 60, 65, and 70 minutes after cannabis use to explore how pupil response changes as the acute effect of cannabis consumption fades.

2. Methods

2.1 *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 consume 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", and 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 provided in Brooks-Russell et.al. (Brooks-Russell et al., 2021)

Videos of pupil response during the light test were collected using SafetyScanTM infrared videography goggles developed by Ocular Data Systems. 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. (Steinhart et al., 2023) . 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.

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. Time between cannabis consumption and the pupil light response test varied from 53 – 84 minutes with a mean of 62.2 minutes (see Figure 4A).

[Table 1 about here.]

2.2 *Functional Data Analysis*

Functional data analysis (FDA) is a field of statistics that models full trajectories without extracting pre-defined specific features. It examines differences in the patterns of the trajectories as they relate to an outcome, such as differences in the pupil light response trajectory that inform whether a person has recently consumed cannabis. The term "functional" in FDA refers to the structure of the data as a function over time instead of a characteristic of the participant or covariates. In our analysis, a single functional unit is the pupil 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 modelled as the outcome or covariate, with t specifying the time at which the measurement was assessed. For example, if participant 1 has the pupil light response trajectory shown in Figure 1, with pupil change of -25.3% at 2 seconds after the start of the light test, then $y_i(t) = y_1(2) = -25.3$. Similarly, at 5 seconds after the start of the light test $y_1(5) = -14.9$.

Our analysis uses two distinct FDA methods to model differences in pupil response to light after cannabis use. The first method, functional logistic regression, is used to predict recent cannabis use and treats the pupil response trajectory as a covariate. 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 pupil light response trajectory as the outcome. These methods and their roles in this analysis are described in more detail below.

2.3 *Predicting recent cannabis use*

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 (Ramsay and Silverman, 2005; Reiss et al., 2017) relates binary responses y_i (e.g.

recent cannabis use vs. no use) to functional covariates $x_i(t)$ (the pupil response trajectory for the i^{th} participant). This model is analogous to logistic regression and is given by

$$logit(P(y_i = 1)) = \beta_0 + \int_t \beta_1(t)x_i(t) \tag{1}$$

As with traditional logistic regression, the coefficient $\beta_1(t)$ 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 t during the pupil light response test. When exponentiated, $\beta_1(t)$ is interpreted as an odds ratio at each time t. This model can be used to predict recent cannabis use using the full pupil 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 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 (Steinhart et al., 2023) 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 pupil 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.

2.4 *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 $y_i(t)$ to scalar covariates x_i (e.g. age, cannabis use group, gender). The FoSR model is

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

Coefficients $\beta_0(t)$, $\beta_1(t)$, and $\beta_2(t)$ are akin to regression coefficients in linear regression, with the added advantage that they are defined at each time t during the pupil light response test. The intercept $\beta_0(t)$ is interpreted as the average trajectory of a participant in the no use control group. $\beta_1(t)$ is the average difference at a specific time t between the occasional use and no use groups, and $\beta_2(t)$ is the average difference between the daily use and no use groups. The error term $\epsilon_i(t)$, like in traditional linear regression, is normally distributed and independent across participants. Unlike traditional linear regression, the errors may be correlated over time t.

2.4.1 *Modeling the effect of a time delay from cannabis use to testing pupil light response.* The time from cannabis use to the pupil 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

$$y_i(t) = \beta_0(t) + \beta_1(t)I(recent\ use) + \beta_2(t)I(recent\ use) * TD + \epsilon_i(t) \quad (3)$$

where $y_i(t)$, $\beta_0(t)$, and $\epsilon_i(t)$ 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 time delay from cannabis use to testing, and

$\beta_2(t)$ is the average difference at a specific time t for an additional minute increase in time since smoking for the cannabis use group.

2.4.2 *Analysis Software.* All analyses were conducted using R version 4.0.2 (2020-06-22) (R Core Team, 2020). The R packages mgcv (Wood, 2011) and refund (Goldsmith et al., 2023) were used to implement functional data models. Code for reproducing our analysis is publicly available on GitHub.

3. Result

3.1 *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 pupil 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.

[Figure 2 about here.]

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 decrease the odds of being in the cannabis use group.

3.2 *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 somewhat 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.

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 pupil 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 pupil light response in our data.

[Figure 3 about here.]

3.3 *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 as the acute effect of cannabis consumption fades.

The number of minutes from cannabis consumption to administration of the pupil 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 consumption 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. As time since cannabis consumption increases, the point of minimal constriction approaches that of the no use group while the rebound dilation appears to remain distinct.

[Figure 4 about here.]

4. Discussion

It is necessary for occupation health and traffic safety settings to establish a tool that can detect recent cannabis use. While there have been multiple efforts to define tests for recent cannabis use, many have suffered from tolerance effects with regular cannabis consumption. The current analysis provides evidence that pupil 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. Additionally, FDA methods allow visualization and statistical

comparison of the average pupil responses across cannabis use groups. We found significant differences in pupil response 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. Taken together, this provides promising evidence that the pupil light response trajectory is a measure of recent cannabis use that is robust to the tolerance effects of frequent cannabis consumption. We were also able to model and visualize how pupil response trajectories change as time since cannabis consumption increases.

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 pupil light response there were a minority that were removed because there was 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, it was not feasible to estimate the absolute pupil diameter in millimeters due to improper fit of the pupil tracking googles used in the study; percent change is reported instead. Currently, we are collecting data on a large sample with a better validated pupillometer device and will replicate this analysis in that sample. However, it speaks to the robustness of our analysis that significant differences were still detected.

Lending support to the robustness of these results are comments from participants relayed by investigators that the participants did not over consume cannabis during the testing, and they did not get as "high" as they usually do. Although anecdotal, these comments indicate

that the results from this analysis may be conservative, with larger differences seen in real world setting where there is no monitoring of cannabis consumption.

This analysis is the first foray into pairing functional data analysis with pupil light response trajectories to better understand the utility of these methods in detecting recent cannabis use. We are cautiously optimistic that these results show an advantage in using the full pupil light response trajectory to discriminate between cannabis users and a no-use control with only data collected after consumption. With larger samples and better validated data collection methods, functional data analysis methods should lead to tests with high specificity providing accountability, ensuring safer workplaces, and reducing driver impairment on our roads.

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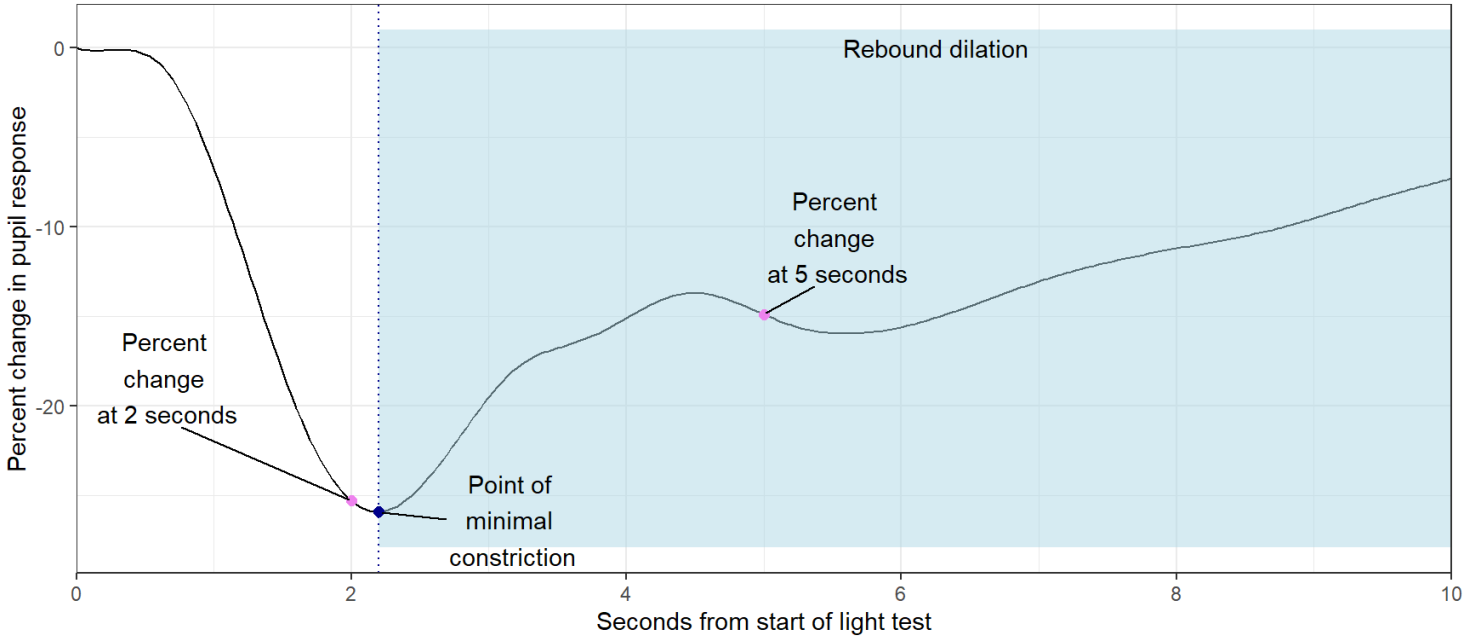

Figure 1. A typical pupillary response to light during the light reflex test, which we refer to as a *pupil light response trajectory* throughout the paper. After the light is shined (time 0 on the x-axis) the pupil begins to constrict in size until it reaches a minimum, called the *point of minimal 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*.

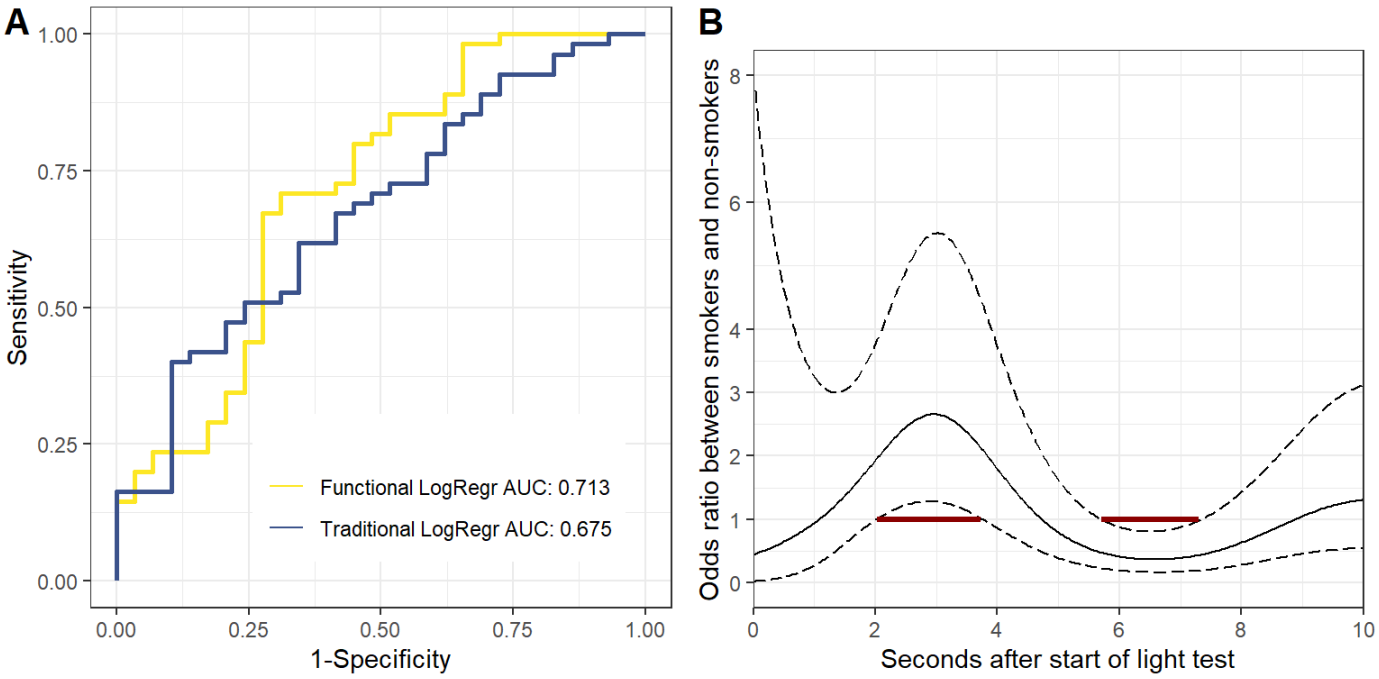

Figure 2. Panel A: Receiver Operator Characteristic curves (ROCs) for our two logistic regression (LogRegr) models. Higher accuracy in predicting recent cannabis use is indicated by a higher AUC and the ROC curve following the left and top edge of the graph. The blue line is an ROC curve for a traditional 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 the 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 pupil 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 recent cannabis use and no use.

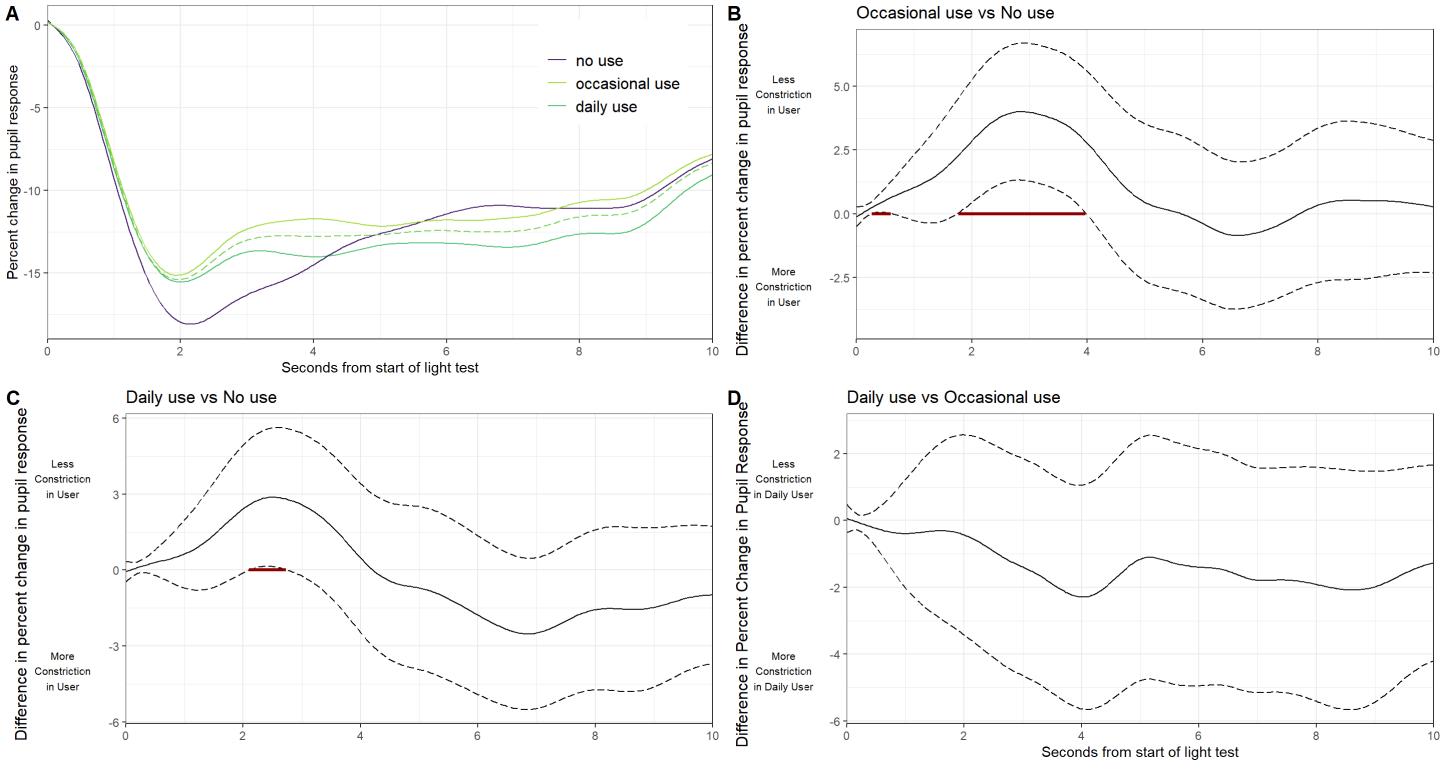

Figure 3. A-D: Panel A shows average pupil light response trajectories plotted by cannabis use frequency. An additional dotted lined based on the average trajectory for all recent cannabis users, occasional and daily, was included to show differences between recent use and no use groups. Panel B shows 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.

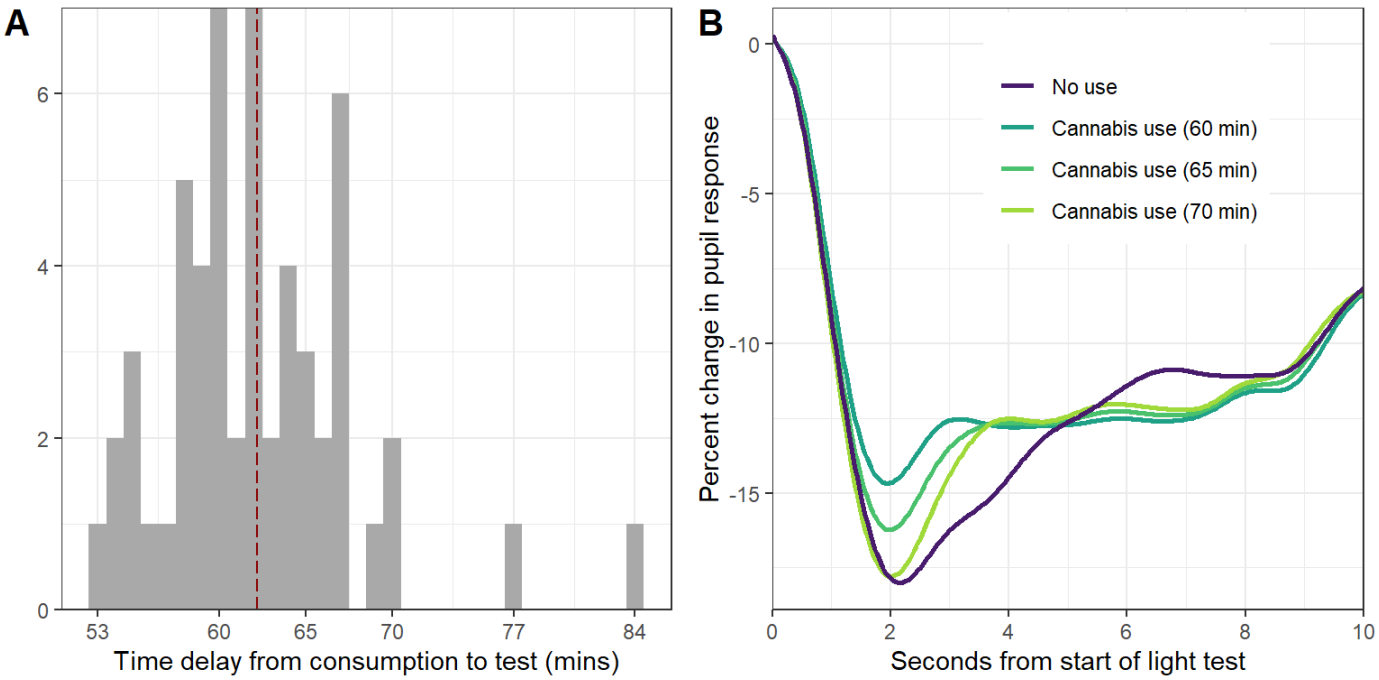

Figure 4. Panel A: Histogram depicts the distribution of the time delay from cannabis use to the pupil light response test, in minutes. The vertical dotted red line indicates the mean of the distribution at 62.2 minutes. Interquartile range is 59 – 66 minutes. Panel B: Differences in the average pupil 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 rebound dilation appears to remain distinct.

Characteristic	Cannabis Use Group			
	No use (N=29)[1]	**Occasional (N = 30)**[1]	**Daily (N = 25)**[1]	**Total (N = 84)**[1]
Age (years)	32.29 (4.70)	31.15 (4.75)	32.75 (5.71)	32.02 (5.02)
Sex				
Female	16 (55%)	10 (33%)	9 (36%)	35 (42%)
Male	13 (45%)	20 (67%)	16 (64%)	49 (58%)
Body Mass Index (kg/m^2)	24.94 (4.72)	24.49 (3.96)	27.08 (4.26)	25.42 (4.41)
THC, post consumption (mg/dL)	0.00 (0.00)	9.52 (12.20)	34.91 (37.26)	13.84 (25.82)
Time delay post consumption (mins)	0.00 (0.00)	63.93 (6.26)	60.16 (3.78)	40.74 (30.10)

[1] Mean (SD); n (%)

Table 1
Participant Sample Characteristics