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

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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 [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 [1], and while cannabis consumption at- or before- work is of concern to employers with regards to occupational injury, the literature on the topic is mixed [2, 3] with temporality of exposure being a major concern. However, there is strong biological evidence of the impairment caused by cannabis consumption depend on the route of administration [4]. To better understand the impairment of cannabis in driving and in the workplace an impairment test is needed.

There are a variety of tests that may have the potential to detect impairment under the influence of cannabis; however, many of these tests have shown a reduction in effectiveness when administered on frequent cannabis users. A more general test used for alcohol and drug impairment is the Standardized Field Sobriety Tests, which is composed 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 [5]. While shown to an accurate and reliable assessment for alcohol impairment, it has limited ability to identify drug use [5]. 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 daily users [6]. Additionally, for frequent users who maintain elevated levels of blood plasma THC, the reduction in performance shows a tolerance effect so that the levels of THC and performance correspond less [6].

One test that may have a resistance to the tolerance effect is the pupillary light reflex. This test is administered by shining a light in the eye of the subject and measuring the pupil constriction and rebound dilation over the course of several seconds as shown in Figure 1. Evidence on the acute effect of cannabis on pupillary light reflex is mixed with several studies showing decrease, increase and no effect on the static pupil diameter [7-13]. In two studies, the pupillary light reflex was diminished after cannabis consumption [8, 14]. There is some evidence that there is less pupil constriction and slower rebound dilation due to acute cannabis consumption but evidence is mixed and warrants further study.

Steinhart et al [15] examined pupil light response in participants with patterns of daily cannabis use, occasional cannabis use, and a no-use control group. After accounting for pre-smoking baseline pupil response, they found evidence that acute cannabis consumption was significantly associated with less pupil constriction in both the daily and occasional use groups. In addition, no significant differences were found between the daily and occasional use groups, indicating that the pupil light response may pick up on physiological responses to cannabis consumption that do not display tolerance effects. However, that study only found significant effects when accounting for pre-smoking baseline pupil response, making it inappropriate for roadside assessments where baseline measurements are not available. In addition, Steinhart et al [15] used single number summaries extracted from the full pupillary response trajectories depicted in Figure 1; collapsing these trajectories results in a loss of information that could potentially be exploited to better discriminate between cannabis use groups.

Using only data from after acute cannabis use, this analysis leverage full pupil light response trajectories to examine differences between cannabis use groups and no use controls.. First, we will compare the ability of a model using the full trajectory of the pupil light response versus a model using single values feature summaries to discriminate between the cannabis use group and the no-use control group. Second, we will estimate differences in the pupil light response based on self-reported cannabis use frequency categories and finally we examine the effect of a time delay in testing after cannabis use on estimating full trajectories of the pupil light response.

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, and participant enrollment as well as screening criteria are described in Brooks-Russell et.al., 2021. [16] 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 day 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.

Videos of pupil response during a light test were collected using SafetyScanTM infrared videography goggles developed by Ocular Data Systems. Trajectories of pupillary light response like that shown in Figure 1 were extracted from the videos using the video segmentation pipeline described in Steinhart et al, 2023. These trajectories represent percent change from baseline values of pupil size for each eye post cannabis consumption (occasional and daily use groups) or a short rest period (no use control group). Pupillary light reflex 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 a no-use group, and 30 and 25 participants in 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); an average BMI of 25.4 kg/m2 (sd. 4.41); and 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 median of 62 minutes (see Figure 4).

*Functional Data Analysis*

Functional data analysis (FDA) is a field of statistics that models curves or trajectories of information without extracting pre-defined specific features. It allows examination of differences in the patterns of the curves as it relates to an outcome, and how the patterns of the curves differ based on individual characteristics. Our analysis uses two distinct FDA methods to model differences in pupil response to light across cannabis groups; these models differ in whether the pupil response trajectory is treated as a covariate or the outcome.

The first method is known as scalar-on-function regression (SoFR)[17, 18] in the FDA literature, and treats smoker vs. non smoker as a binary outcome with pupil response trajectory as a covariate. This model is analogous to logistic regression and is given by

ADD SoFR Model here

[more details] In this analysis, a SoFR model will be used to determine the subtle differences in the pupillary light reflex that discriminate between cannabis use group versus nouse group.

The second FDA method used is function-on-scalar regression (FoSR), which 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

ADD FoSR Model here

[Add details that explain fosr model similar to the details for SoFR]

FoSR models will be used to distinguish pupil trajectory patterns that are associated with acute cannabis use in the daily and occasional use groups with pupil trajectory patterns associated with no use.

Additionally, due to the variability in the time from cannabis consumption to the post test, a FoSR model was used to explain differences in trajectories due to cannabis use frequency and time differences in wait time between cannabis use and testing.

*Prediction Analysis*

The goal of this portion of the analysis is to build a model that best discriminates between those who recently smoked cannabis (designated “cannabis use” group, combines daily and occasional use groups) and those who did not (designated “no use”). Our main model is the SoFR functional logistic regression model described above; we compare the to a 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) AUC, 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 cannabis use status, and expect better prediction from the SoFR model because it leverages information from the full pupil response trajectories. Receiver operating characteristic curves (ROCs) for each model were used to assess the accuracy of the models with area under the curve.

Analysis Software

All analyses were conducted in R (version 4.0.2).[19] The R packages mgcv[20] and refund [18]were used for functional data models.

RESULTS:

Table 1:

|  | **Cannabis Use Group** | | |  |
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|  | **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) |
| 1Mean (SD); n (%) | | | | |

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| Figure 1: |

The ROC curves for the prediction analysis compared the discrimination ability for two models; one uses summary features of the trajectory of the pupillary light reflex and the second used the full trajectory of the pupillary light reflex (Figure 1). The AUCs, used to quantify the discrimination ability of the model, for these prediction models ranged from 0.68 to 0.71, with the model using the full trajectory of pupillary light reflex having the higher AUC. This indicates that models using full trajectory information of pupillary light reflex may have the ability to discriminate between cannabis smokers and non-smokers better than feature-based models.

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| Figure 2A: Receiver Operator Characteristic curves (ROCs) for our two logistic regression 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 model depicted with the blue line was constructed with summary features of pupillary light reflex which included the point of minimal constriction, the area under the curve after the point of minimal constriction and the rebound dilation slope after the point of minimal constriction. The model depicted with the yellow was constricted with the full trajectory of pupillary light reflex without creating summary features. Although similar, the model utilizing the full trajectory data has better discrimination ability between smokers and non-smokers.  Figure 2B: The dashed lines indicate the point wise 95% confidence interval around the Odds Ratio (OR) estimate.  The plot depicts the odds ratio (OR) of being a smokers vs non-smokers across the time course of the pupillary light reflex. High ORs would increase the probability of predicting a smoker. The red dotted segments indicate areas where the confidence interval (both dashed lines) are above or below critical value, demonstrating statistically significant differences between smokers and non-smokers. |

Because the functional logistic regression model in the yellow line of Figure XX (1 now, but will become Figure2A) leverages information in the full pupil response trajectories it is better able to discriminate between participants who have recently used cannabis from those who have not. An added benefit of this model is the ability to visualize the odds of cannabis use over the 10 seconds of the pupil light response test (Figure 2). This plot shows…, and statistically significant differences are seen between 2.03 and 3.73 seconds with a maximum difference at 2.97 seconds (OR: 2.66, 95% CI: [1.28, 5.50]) and between 5.7 and 7.3 seconds with a peak difference at 6.57 seconds (OR: 0.37, 95% CI: [0.17, 0.81]).

The FoSR model was used to show differences between the average trajectories of pupillary light reflex in daily, occasional and no-use groups. A separate model estimated the average trajectory of smokers and non-smokers. In Figure 3, the average trajectories are plotted with solid lines for cannabis use frequency and a dashed line was overlaid for all smokers. The no—use group and non-smokers encompass the same individuals and therefore overlap completely. From the figure, we can see a stronger initial constriction in no-use group and a steady rebound after the light test; however, in smokers of both groups there is less initial constriction, and the slope of the rebound dilation is shallower.

Using the FoSR model, we depict the differences between the average trajectories for occasional and non-users, daily and non-user and daily and occasional users (Figure 4). These plots show regions of significant difference between occasional and non-users as well as daily and non-user; however, there are no significant differences in the average trajectories of daily and occasional users. When comparing occasional and non-user the most prominent differences 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 daily and non-users there is significant difference region in a similar time period from 2.1 to 2.73 seconds with a peak difference at 2.5 seconds of 2.88% (95% CI: 0.14%, 5.62%).

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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 smokers, was included to show differences between use and no-use groups. Panel B shows the difference in average trajectories between pairs of occasional, daily and non-user 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 indicate statistically significant differences between trajectories. The figure demonstrates significant regions of difference between occasional and non-users and daily and non-users; while there is no significant difference between occasional and daily users. |

The effects of the testing delay after cannabis consumption may impact the results of the previous analyses, so we examined the distribution of this testing delay and modelled it’s effects the mean trajectories of smokers at delay times of 60, 65, and 70 minutes from cannabis consumption. The distribution of the testing delay is show in Figure 5. The testing delay ranged from 53 to 84 minutes with a mean of 62.22 minutes (sd = 5.57). Figure 6 depicts the average trajectory of non-smoker and smokers with a 60-, 65-, and 70-minute delay in testing. As shown in the figure, the initial pupil constriction after the start of the light test is reduced in smokers with less delay in testing and reaches constriction similar to non-smoker with a longer delay in testing. However, the slope of the rebound dilation is still shallower in smokers with any of test delay compared to non-smokers.

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| Figure 4: The plot shows the distribution of the time delay from cannabis smoking to the post pupillary light reflex test for cannabis smokers. The red line indicates the mean of the distribution at 62.7 minutes with an interquartile range between 59 – 66 minutes. |

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| Figure 5: The plot depicts the differences in the average pupillary light reflex response as the time from smoking increases from 60 minutes to 70 minutes (lighter color). The red line shows the average trajectory of a non-smoker. With longer delays in the test time, the point of minimal constriction seems to match that of non-smokers while the rebound dilation appears to remain distinct. |

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 and cannabis impairment, many have suffered from tolerance effects with regular cannabis consumption. The current analysis provides evidence that pupillary light reflex, 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, the current modelling paradigm demonstrates differences in trajectories of the pupillary light reflex between non-users and occasional users after cannabis consumptions, and those differences persist between non-user and daily user showing a robustness to the effects of drug tolerance which is not seen with other tests. By examining the effects of time delays from consumption to test, we were able to show that the while time delays mitigated the effect on initial pupil constriction, the differences in the rebound effect were maintained, so that a test focusing on rebound effects may be able to discriminate between smokers and non-smokers.

However, there are several limitations to this analysis for which further analysis and more sophisticated instrumentation 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 pupillary light reflex trajectories reflected the characteristic pattern of the light reflex there were a minority that were removed because there was no characteristic features of the reflex. This led to a reduction in the sample size from a collection of 101 participant to usable data in 84. While it speaks to the robustness of the method that significant differences were still detected, it also limits the precision of the estimated differences. Additionally, due to improper fit of the pupil tracking googles used in the study, it was not feasible to estimate the baseline pupil size of individual, which is directly related to the amount of change pupils can undergo when exposed to a light stimulus. Being unable to account for the baseline pupil size also increases the imprecision in the estimation of differences in pupillary light reflex trajectories by marijuana use frequency.

Limitations:

1. Sample size small
2. Data noisy, no systematic length of light stimulus; recording googles did not fit well on all subjects
3. Prediction analysis did not use an independent test set.

Strength:

1. Participant did not “over” consume cannabis during the test may not have gotten as “high” as they would on a regular basis – but we can still measure an effect difference (not really a limitation)

HOW DOES THIS FIT INTO A LARGE CONTEXT?

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